

REACTIONS OF ALCOHOLS IN
ACETIC ANHYDRIDE-MINERAL ACID MIXTURES

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ABSTRACT

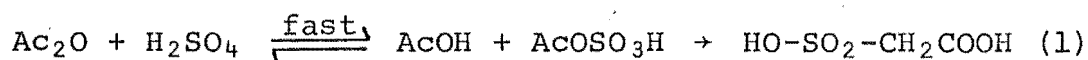
The reaction of 3 β -cholestanol with acetic anhydride and sulphuric acid has been studied. A kinetic investigation has been made of the reaction of these reagents with cyclohexanol, 1-methylcyclohexanol and a series of benzyl alcohols. The relative rates for the reaction of some 6 β -substituted-3 β -acetoxycholestan-5 α -ols in this system have been determined and the rates compared with that for 1-methylcyclohexanol.

The reaction of 3 β ,6 β -diacetoxycholestan-5 α -ol with fluosulphonic acid has been shown to involve a "backbone" rearrangement terminated at a position intermediate between those usually found. The structure of one of the products has been determined and a structure is suggested for another product.

GENERAL INTRODUCTION.

Equilibria between Acetic Anhydride and Inorganic Acids.

The first measurements of the acidities of various acids in acetic acid solution were carried out potentiometrically using chloranil¹ and hydrogen² electrodes. The acidities, $(\text{pH})^{\text{HAc}}$, were found¹ to be greater in acetic acid than in aqueous solutions and were enhanced² even more by the presence of acetic anhydride. The latter enhancement was found to be greatest for sulphuric acid; the acidity increased markedly with increased anhydride concentration up to a certain concentration (8% Ac_2O for 1M H_2SO_4) and then more gradually. This was explained by the formation of a monobasic acid, acetyl sulphate, which slowly decomposed on standing to sulphoacetic acid.



Acetyl sulphate would be expected to be more acidic than sulphuric acid because of the greater stability of the anion caused by the replacement of a hydrogen atom by the electron withdrawing acetyl group.

Perchloric acid showed a gradual increase in acidity with increase in acetic anhydride concentration indicative of some compound formation, while the acidity of sulpho-

acetic acid appeared to be practically independent of acetic anhydride concentration (addition of a further acetyl group would not give an acidic compound).

Further evidence for the suitability of mechanism (1) to explain the behaviour of sulphuric acid-acetic anhydride mixtures came from a kinetic study³ of the rates of formation of sulphoaliphatic acids. Mechanism (1) would predict that the rate would be dependent on the sulphuric acid concentration and the ratio of anhydride to acid.

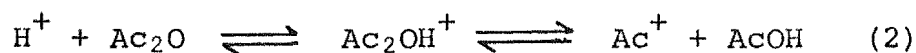
$$\text{rate} = k [\text{H}_2\text{SO}_4] [\text{Ac}_2\text{O}] / [\text{AcOH}]$$

A first order dependence on sulphuric acid was found and a good linear plot of rate vs $[\text{anhydride}] / [\text{acid}]$ was found for propionic and butyric anhydrides. For acetic anhydride and acetic acid deviations from linearity found at higher anhydride concentrations were considered to be due to solvent effects.

Mackenzie and Winter studied⁴ the acetylation of quinones by acetic anhydride catalysed by perchloric acid (Thiele acetylation) and found^{4a} that the rate varied markedly with the ratio of acetic anhydride to acetic acid in the solvent. They measured the acidity of the solvent both by potentiometric methods to give $(\text{pH})^{\text{HAc}}$ and by indicator ionization^{4a,b} to give an acidity function

related to the Hammett H_0 and found that these showed a dependence on the $\text{Ac}_2\text{O}/\text{AcOH}$ ratio similar to that of the rate. However there was no general dependence of the rate on the acidity for different catalysing acids. The suggested mechanism^{4c} involved attack on the quinone by both Ac^+ and AcOH_2^+ ions but the kinetic data were complex and the mechanism has been questioned by later workers.

Burton and Praill⁵ studied the reaction yields for the acetylation of anisole by acetic anhydride and perchloric acid and by acetyl perchlorate. They suggested that the acetylium ion Ac^+ is the principal acetylating agent for both systems with protonated acetic anhydride as a further, less active acetylating agent. In the first system Ac^+ is produced from acetic anhydride according to mechanism (2).

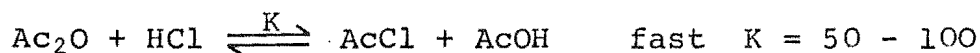


Acetyl perchlorate was considered to exist mainly as an ion pair $\text{Ac}^+\text{ClO}_4^-$ in anisole but to dissociate into Ac^+ and ClO_4^- in solvents of high dielectric constant (nitromethane). The Ac^+ produced reacts with acetic acid to give the secondary acetylating agent by the reverse of mechanism (2).

The previous kinetic evidence of Mackenzie and Winter and Burton and Praill was considered by Satchell⁶ to be rather

inconclusive and therefore a more intensive study of the equilibria between acids and acetic anhydride was initiated.

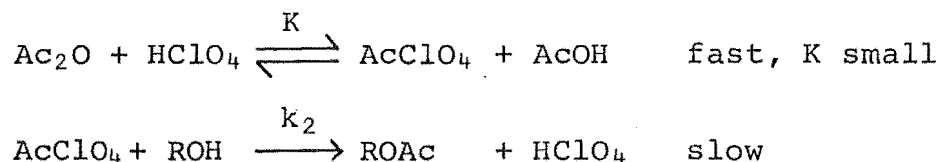
The acetylation of β -naphthol by acetic anhydride and hydrochloric acid showed a first order rate dependence on naphthol and the acid when anhydride was present in excess, and a lower order dependence on [acid] when this was close to the anhydride concentration. This is consistent with the following mechanism.



The same rate was found for acetyl chloride and acetic anhydride-hydrochloric acid at equivalent concentrations which indicates that Ac^+ is the acetylating species, not $\text{Ac}_2\text{OH}^+\text{Cl}^-$. Complete acetyl (C^{14}) exchange between the anhydride and acetic acid was found to occur but the presence of a slight absorption in the infrared due to acetic anhydride showed that the equilibrium constant was not infinite. A similar mechanism was found for hydrobromic acid.

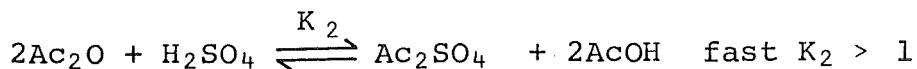
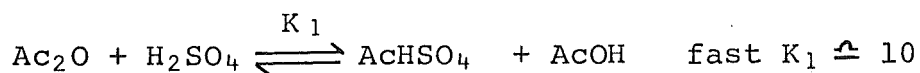
For catalysis of acetylation by perchloric acid the mechanism was found⁶ to be basically similar. The rate showed a first order dependence on both acetic anhydride and perchloric acid, indicating a low value of K , and acetyl perchlorate gave the same rate as a mixture of anhydride and

acid. The mechanism was considered to be as follows.



Ionization data using a Bronsted base indicator (B) showed that $\text{Ac}_2\text{OH}^+\text{ClO}_4^-$ was not an acetylating agent in this system; $\log k_2$ should have been linearly dependent on $\log \frac{[\text{BH}^+\text{ClO}_4^-]}{[\text{B}]}$ if this species was involved. Kinetic study cannot say whether the acetyl perchlorate is present as an ion pair $\text{Ac}^+\text{ClO}_4^-$ or as a compound AcClO_4 .

A different behaviour was found⁷ for catalysis of acetylation by sulphuric acid. *m*-Nitrophenol was used as the substrate for kinetic studies since sulphonation occurs for β -naphthol. The rate dependence on anhydride was greater than unity, about 1.5 for acetic anhydride and 1.3 for butyric anhydride. If the equilibrium constant, K , for the formation of acetyl hydrogen sulphate AcHSO_4 was high the rate would not show a dependence on Ac_2O when this was present in excess, while if K was very small the dependence would be first order. The suggested mechanism involved the existence of two equilibria to give two reactive species, AcHSO_4 and Ac_2SO_4 .



The observed kinetics require the participation of both reactive species, the rate constant being greater for Ac_2SO_4 .

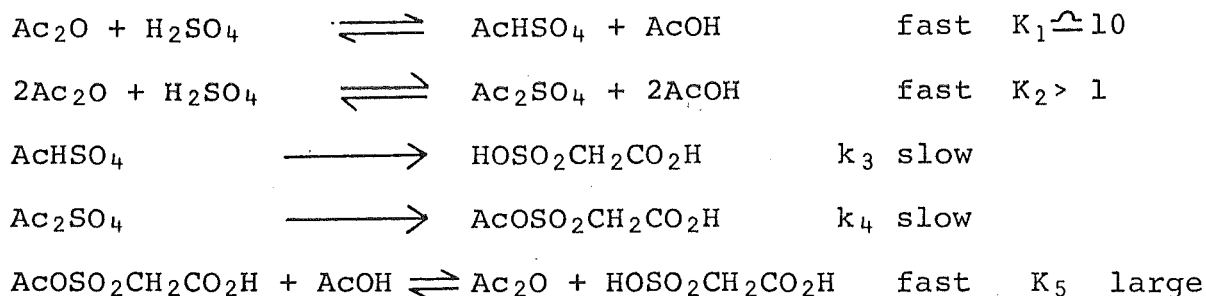


The infrared spectrum of a mixture of acetic anhydride, acetic acid and sulphuric acid showed the presence of an absorption not due to any of these compounds; this confirmed the existence of a new species, AcHSO_4 .

Catalysis of sulphoacetic acid was found⁷ to be similar to that by perchloric acid, the equilibrium favouring sulphoacetic acid, not the reactive species.

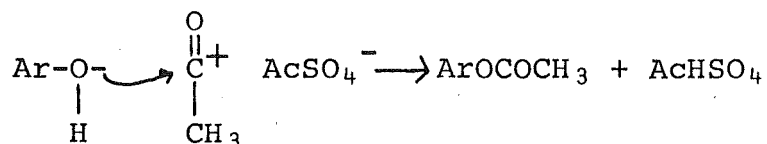
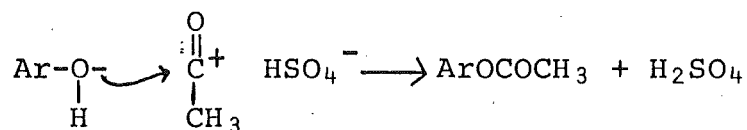
The mechanism of the formation of sulphoacetic acid from sulphuric acid and acetic anhydride was studied⁸ by carrying out the kinetic measurements under more satisfactory conditions than those of Murray and Kenyon (lower anhydride concentrations). The rate was found to show a first order dependence on H_2SO_4 and an order greater than unity for the dependence on anhydride. The dependence on anhydride was found to be the same as for acetylation and a plot of the rate of acetylation against the rate of formation of sulphoacetic acid under the same conditions was linear. Two intermediate, AcHSO_4

and Ac_2SO_4 were postulated to be common to the two reactions and the following mechanism was proposed.

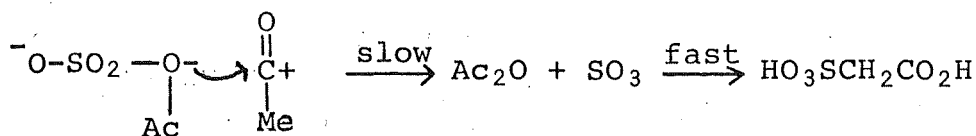
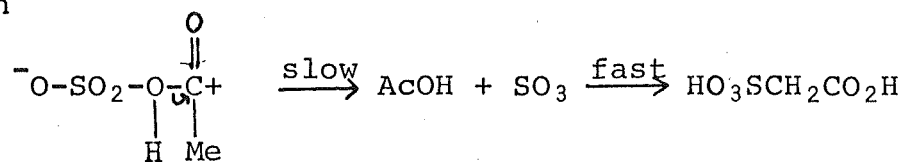


The correlation between the two sets of k values indicated that the relative reactivities of the two intermediates were the same in both reactions so similar mechanisms were proposed for the slow steps of the two reactions. Both mechanisms involved the ionized forms of the two sulphates which would be in equilibrium with the unionized forms.

Acetylation



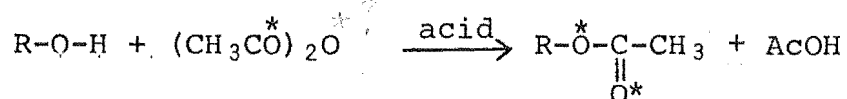
Sulphoacetic acid formation



The reaction of sulphur trioxide and acetic acid suggested for the second reaction was known to be fast but there is no direct evidence of its involvement here.

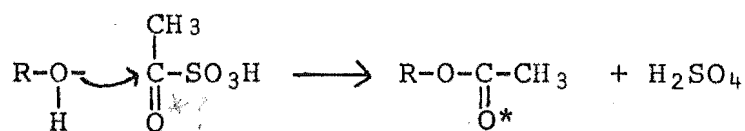
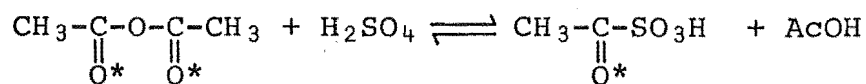
Reactions of Alcohols with Acetic Anhydride and Inorganic Acids.

In acetylation reactions of alcohols with mixtures of an inorganic acid and acetic anhydride two general types of mechanism are to be anticipated. The first involves alkyl-oxygen fission; both oxygen atoms in the product acetate are derived from the acetylating system.



This mechanism can also lead to elimination products if carbonium ion formation is involved.

In the second mechanism acyl-oxygen fission occurs in the acetylating species; the hydroxyl oxygen present in the reactant alcohol remains in the product ester as the alkyl oxygen.



Elimination to give olefinic products cannot occur by this mechanism.

Steroid Alcohols - The Westphalen Rearrangement.

Reaction of 3 β , 6 β -diacetoxycholestan-5 α -ol (1a) with acetic anhydride containing sulphuric acid⁹ or potassium hydrogen sulphate¹⁰ as an acidic catalyst was found to give, instead of the expected triacetate (2a) a diacetate of an unsaturated diol. This diol was later shown¹¹ to be 5 β -methyl-19-nor-cholest-9(10)-en-3 β ,6 β -diol (3a). Reaction with p-toluenesulphonic acid¹², hydrochloric acid¹³, hydrofluoboric acid¹⁴, perchloric acid¹⁴ or sulphoacetic acid¹⁴ in acetic anhydride at room temperature gave only the 5 α -acetate (2a).

It was initially assumed that the reaction proceeded via initial protonation of the hydroxy group. However 3 β , 6 β -diacetox-5 α -methoxy-cholestane did not react under similar conditions¹⁴; this mechanism must therefore be excluded. 3 β , 5 α , 6 β -triacetoxycholestan-5 α -ol (2a) did not rearrange¹⁴ under conditions that caused the 5-hydroxy compound (1a) to rearrange in less than 5 minutes. The reaction cannot therefore proceed by initial formation of the 5 α -acetate. This suggested that formation of the carbonium ion proceeded via some derivative of the 5 α -hydroxy group which could only form in the presence of acetic anhydride and sulphuric acid or potassium hydrogen sulphate.

Reaction of cholesterol with sulphuric acid-acetic anhydride was found to give a sulphate ester. Therefore it was suggested¹⁴ that the hydrogen sulphate ester of the 5 α -alcohol was a reaction intermediate, providing a better leaving group for carbonium ion formation than the original hydroxy group.

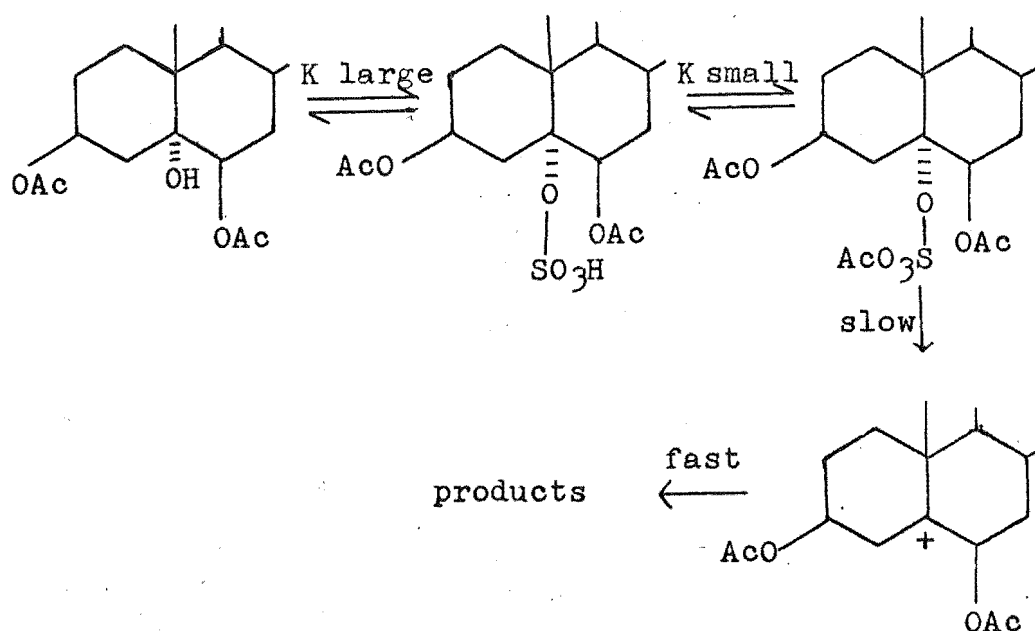
The kinetics of the reaction of 3 β , 6 β -diacetoxycholestan-5 α -ol (1a) with acetic anhydride-sulphuric acid were studied¹⁴. The rate was found to be first order in steroid when the catalysing acid was present in excess and first order in sulphuric acid when the steroid was present in excess. This suggested the existence of a rapid complete equilibrium between one molecule of sulphuric acid and one molecule of steroid to give a steroid hydrogen sulphate. If the equilibrium for intermediate formation favoured the reactants rather than the product or if the intermediate were formed in a slow step then the rate would show a first order dependence on both acid and steroid at all concentrations.

The rate was also found to show a first order dependence on acetic anhydride at low anhydride concentrations and a dependence of order greater than unity at higher concentrations. This indicated that the reaction involved the formation of an acetyl sulphate

ester of the 5 α -hydroxy group. This ester would be expected to be a better leaving group than the hydrogen sulphate ester because of the greater stability of the anion produced - shown by the fact that acetyl sulphuric acid has a higher acidity than sulphuric acid². Since the rate was dependent on the concentration of anhydride even when this reagent was present in excess, formation of the acetyl derivative could not take place in a rapid complete equilibrium and must either be the rate determining step or involve an equilibrium lying largely towards the hydrogen sulphate. This step would be expected to be faster than the succeeding carbonium ion formation; the formation of acetyl hydrogen sulphate and diacetyl sulphate from sulphuric acid and acetic anhydride has been shown to be fast⁷ and the formation of the acetyl derivative of the steroid hydrogen sulphate should be of comparable speed. Therefore the equilibrium forming the acetyl derivative must favour the starting material more than the products.

The rate of the reaction has been shown to be very sensitive to the electronic properties of the substituent group at C-6^{14,15} and C-3¹⁶. Formation of the acetyl derivative would be expected to be insensitive to substituent effects as is the acid catalysed esterification of carboxylic acids¹⁷; the reaction site is

remote from the substituents so the effects of their electronic properties should be small. From Hammett plots of the logarithm of the relative rates against Taft's σ^* values¹⁸ for the 6β and 3β substituents ρ^* values of the order of -3 were calculated. These values were compared with those for other reactions involving carbonium ion formation including the solvolysis of secondary carbinyll *p*-bromobenzene-sulphonates at 70° in acetic acid (-3.5) and the solvolysis of tertiary alkyl chlorides in 80% ethanol at 25° (-3.3)¹⁹. The correlation with these values indicated that the rearrangement proceeded via rate determining carbonium ion formation. The following reaction mechanism was suggested.



In addition to the rearranged material (3), the Δ^4 -unsaturated compounds (4) and the 5α -acetates (2) were obtained in proportions which depended on the nature of the 6β -substituent. Formation of these products is consistent with intervention of an intermediate carbonium ion which may rearrange, suffer proton loss or be captured by acetic acid and thus lead to acetylation via alkyl-oxygen fission.

The formation of the 5α -acetate as the major product when the other acids were used as catalyst appears to involve acyl-oxygen fission with attack by the 5α -hydroxy group on the acetyl group of the acetyl derivative of the catalysing acid since alkyl-oxygen fission would be expected to lead to olefin formation for the other acids also. It appears that these acids cannot react rapidly and completely with the alcohol to form an ester as sulphuric acid is considered to do.

PART I

REACTIONS OF ALCOHOLS WITH SULPHURIC
ACID AND ACETIC ANHYDRIDE

INTRODUCTION

The reactions of certain 5 α -hydroxy steroids with acetic anhydride catalysed by sulphuric acid have been shown to proceed by formation of a sulphate ester followed by alkyl-oxygen fission to give a carbonium ion (see General Introduction). However for catalysis by other acids the reaction is considered to proceed by acyl-oxygen fission.

It therefore appeared worthwhile to investigate the reactions of other alcohols, primary, secondary and tertiary, with the sulphuric acid-acetic anhydride system to ascertain which mode of fission, alkyl-oxygen or acyl-oxygen was required to explain the observed rate dependence or products.

The products of acetylation of a steroid secondary alcohol, β -cholestanol, were studied. Thorough kinetic investigations of the acetylation of cyclohexanol and benzyl alcohol were carried out and a comparison of the rates of various substituted alcohols made. The reaction of 1-methylcyclohexanol, a tertiary alcohol, with acetic anhydride-sulphuric acid was studied and its rate of reaction was compared with those of some 5 α -hydroxy steroids. The relative rates for some 5 α -hydroxy steroids previously published by Fischer et al. have been redetermined. Some isotopic substitution work using acetic acid containing O¹⁸ has been carried out on a few alcohols to confirm the conclusions obtained from kinetic data and product analyses.

EXPERIMENTAL

Melting points are uncorrected. Optical rotations were determined for chloroform solutions unless another solvent is specified. Infrared absorption measurements were carried out in carbon disulphide solutions and recorded with a Perkin Elmer model 137 or 337 instrument. Alumina used for chromatography was Peter Spence, Grade H, deactivated by the addition of 5% of 10% aqueous acetic acid (unless otherwise stated). Light petroleum refers to the fraction of b.p. 50-70°. Silica gel was used for TLC. Chloroform-acetone mixtures were used for developing chromatograms and the visualising agent used was antimony trichloride in chloroform.

3 β -Cholesterol²⁰ (6a)

To a solution of cholesterol (30g) in ethyl acetate (450ml) were added platinum oxide (Adams catalyst; 0.9^o) and perchloric acid (1 drop). The resulting suspension was stirred vigorously in a hydrogen atmosphere at 40^o until uptake of hydrogen ceased. The system was flushed with nitrogen and the HClO₄ neutralised by adding aqueous NaOH (0.2ml, 12.5N). The solution was filtered hot to remove the catalyst. Removal of solvent to half the volume gave, on cooling β -cholestanol (26g), m.p. 139-140^o, $[\alpha]_D + 23^o$ (c 1.0). (Lit.²⁰ m.p. 139-141^o, $[\alpha]_D + 24^o$).

3 β -Acetoxycholestane (6b)

To a solution of 3 β -cholestanol (1g) in dry pyridine (15ml) was added acetic anhydride (1m) and the mixture allowed to stand overnight. It was further reacted by heating at 60^o

for 8 hrs. The product was isolated via pentane-water and removal of solvent and recrystallisation from methanol gave 3 β -acetoxycholestane (1.05g), m.p. 108-109 $^{\circ}$, $[\alpha]_D + 12^{\circ}$. (Lit.²¹ m.p. 109-110 $^{\circ}$, $[\alpha]_D + 13^{\circ}$).

3 β -Cholestanol p-toluenesulphonate²² (6d)

To a solution of 3 β -cholestanol (5g) in dry pyridine (10ml) was added p-toluenesulphonyl chloride (5g) and the mixture allowed to stand overnight at room temperature. The steroidal material was isolated via chloroform and adsorbed onto 25g activated alumina. Elution with chloroform followed by removal of solvent and crystallisation from acetone gave 3 β -cholestanol p-toluenesulphonate (4.5g), m.p. 132-133 $^{\circ}$. (Lit.²³ m.p. 136-137 $^{\circ}$).

3 α -Cholestanol²³ (7a)

A solution of 3 β -cholestanol p-toluenesulphonate (2g) in t-butanol (150ml) was refluxed for 68 hrs. After removal of the solvent, isolation via ether gave a solid which was adsorbed onto 50g alumina.

Elution with light petroleum gave unreacted p-toluenesulphonate (560mg).

Elution with light petroleum-benzene (1:1) gave 3 β -cholestanol (440mg).

Elution with benzene gave 3 α -cholestanol (277mg), m.p. 182-183 $^{\circ}$. (Lit.²³ m.p. 185-185.5 $^{\circ}$).

3 α -Acetoxycholestane (7b)

To a solution of 3 α -cholestanol (200mg) in dry pyridine (10ml) was added acetic anhydride (0.2ml) and the mixture allowed to stand at room temperature overnight. It was further reacted by heating at 60 $^{\circ}$ for 9 hrs.

Isolation of the product in the usual manner

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gave a solid which was adsorbed onto 25 g alumina.

Elution with light petroleum gave 3 α -acetoxycholestane (178mg), shown by tlc to be pure compound, m.p. 91-92°. (Lit.²¹ m.p. 94-95°).

3 β -Cholesterol hydrogen sulphate (6c)

To a solution of 3 β -cholesterol (1g) in carbon tetrachloride (25ml) was added¹⁴ concentrated sulphuric acid (36N, 0.15ml) in acetic anhydride (20ml) and the mixture kept at 20° for 1 min. Pyridine (2ml) was added and the suspension diluted with ether-pentane (1:1, 100ml). Filtration allowed the separation of the pyridinium salt of 3 β -cholesterol hydrogen sulphate (1.36g), m.p. 209° dec. A solution of the pyridinium salt (1.36g) in water (25ml) was treated with potassium iodide (2.5g) in water (20ml). The deposited potassium salt was isolated by filtration, m.p. 212-215° (dec). (Lit.²¹ m.p. 236° (dec.)).

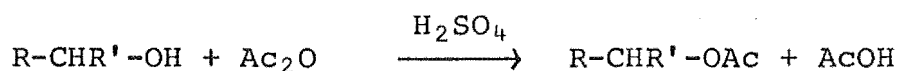
Reaction of 3 β -cholesterol with sulphuric acid-acetic anhydride.

A solution of the steroid (700mg) and sulphuric acid (180 mg) in acetic acid-acetic anhydride (4:1, 25ml) was kept at 20° for 16 hrs. Isolation via pentane gave crude 3 β -acetoxycholestane (6b) (537mg), m.p. 100-102°. Further crystallisation from methanol gave an analytical sample, m.p. 107-109°. (Lit.²¹ m.p. 109-110°).

KINETICS.Introduction.

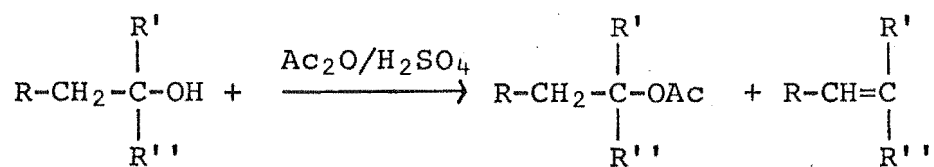
The reaction of acetic anhydride and sulphuric acid with a series of alcohols has been studied in acetic acid at 25°.

For primary and secondary alcohols the reaction is:

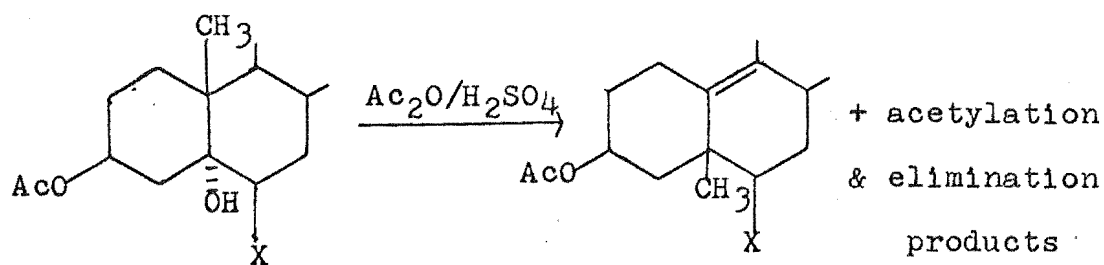


The reactions of most of these alcohols show a first order rate dependence on alcohol.

For tertiary alcohols the reaction is more complex, leading to olefinic products in addition to the acetates.



For steroidal alcohols methyl migration may occur together with elimination.



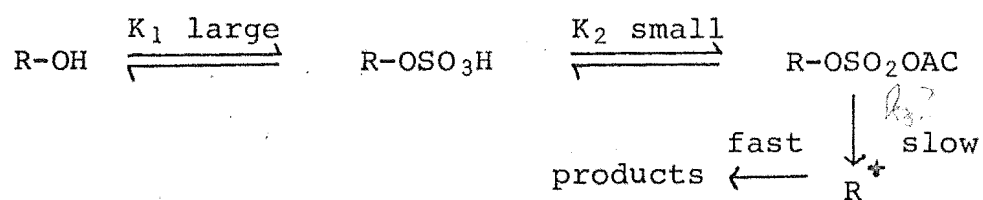
1a X = OAc

3a X = OAc

b X = OCH₃b X = OCH₃c X = H₃d X = CH₃

Compounds 1a and 1b were found¹⁴ to give a mixture of compounds 2, 3 and 4 while the 6-deoxy and 6 β -methyl compounds (1c & 1d) gave no noticeable amounts of compounds 2 or 3 but only the elimination products 4 and 5 (see page 26).

If a mechanism involves carbonium ion formation then the rate can be shown to be zeroth-order in either alcohol or sulphuric acid.



Since K_1 is large, the concentration of ROSO_3H is equal to $[\text{ROH}]$ or $[\text{H}_2\text{SO}_4]$, whichever is the least. So the rate is given by:

$$\begin{aligned}\text{rate} &= k_3 [\text{ROSO}_2\text{OAc}] \\ &= k_3 K_2 [\text{ROSO}_3\text{H}] [\text{Ac}_2\text{O}] / [\text{AcOH}]\end{aligned}$$

If the alcohol is present in excess over sulphuric acid then the reaction can be expected to be zeroth-order in alcohol with rate equal to $k_3 K_2 [\text{H}_2\text{SO}_4] [\text{Ac}_2\text{O}] / [\text{AcOH}]$.

Theory

For a reaction which is first order with respect to one reactant (the others not being consumed during the reaction) we have

$$\frac{dx}{dt} = k(a-x)$$

where x is the concentration of the product at time t , a is the initial concentration of the reactant and k is a pseudo-first order rate constant which includes the effect of the catalyst and excess reagent.

$$\frac{dx}{(a-x)} = k dt$$

On integration this gives

$$-\ln(a-x) = kt + c$$

When $t = 0$, $x = 0$ so

$$0 = - \ln a$$

$$\therefore kt = \ln a - \ln (a-x)$$

This is the integrated rate equation and from a plot of $\log (a-x)$ vs t , which has a slope of $\frac{-k}{2.303}$, the rate constant k may be evaluated.

For a reaction which is zeroth-order with respect to all reactants used up in the reaction we have

$$\frac{dx}{dt} = k \quad (1)$$

On integration this gives

$$x = kt + c \quad (2)$$

When $t = 0$, $x = 0$ so $c = 0$. Therefore from a plot of x vs t , which has a slope of k , the rate constant k may be evaluated.

Preparation of Reagents.

Acetic acid

Acetic acid (BDH "AnalaR" Grade) was dried by azeotropic distillation with benzene²⁴ through a 6 ft column packed with glass helices, followed by distillation through a Vigreux column, the fraction boiling at 118° being collected.

Acetic anhydride

Acetic anhydride (Reidel de Haën AR Grade) was refluxed over magnesium turnings⁶ and fractionally distilled, the fraction boiling at 136-137° being collected.

Sulphuric acid

Sulphuric acid ("AnalaR" Grade) was used without further purification.

Cyclohexanol

Cyclohexanol (BDH Lab. Grade) was dried over molecular sieves (4A) and fractionated through a spinning band column, the fraction boiling at 160-161° being collected and shown to be pure by glc.

Benzyl alcohol

Benzyl alcohol (May and Baker) was dried over molecular sieves (4A) and distilled through a Vigreux column, the fraction boiling at 104-106° (20mm) being collected and shown to be pure by glc.

p-Nitrobenzyl alcohol.

To a stirred solution of p-nitrobenzaldehyde (30.2g) in ethanol (300ml) was added sodium borohydride (4g) in water (30ml) containing sodium hydroxide (0.2g). The mixture was allowed to stand for 2 hrs and then poured into a brine solution. Isolation via ether followed by crystallisation from carbon tetrachloride gave p-nitrobenzyl alcohol (20.6g), m.p. 93-94°. (Lit.²⁵ m.p. 93°).

p-Anisyl alcohol

To a stirred solution of p-methoxybenzaldehyde (0.1m, 13.6g) in ethanol (200ml) was added sodium borohydride (2g) in water (20ml) containing NaOH (0.1g) and the mixture stirred for 2 hrs. NaOH (5g) was added, the mixture heated to near boiling, cooled and left overnight before being poured into brine. Extraction with ether was followed by removal of the solvent; the residue was poured into ether and washed with water. Isolation followed by distillation at 20 mm (b.p. 145°) gave p-anisyl alcohol, shown by IR to be free of aldehyde,

m.p. ca 25°. (Lit.²⁵ m.p. 25°).

p-Methylbenzyl alcohol

(a) p-Methylbenzyl bromide

p-Xylene (26.5g) was added to N-bromosuccinimide (35.6g) in carbon tetrachloride (250ml). Benzoyl peroxide (300mg) was added and the mixture refluxed on a steam bath until the succinimide formed had all settled on top of the solution. The solid material was removed by filtration and the solution concentrated by distillation at 20 mm pressure. Distillation at 15 mm gave p-methylbenzyl bromide (22.3g).

(b) p-Methylbenzyl alcohol

p-Methylbenzyl bromide (22.3g) was added to a solution of sodium carbonate (25g) in water (300ml) and the mixture refluxed for 20 hrs. Isolation via ether followed by distillation at 20 mm gave p-methylbenzyl alcohol (6.4g), m.p. 58.5-59.5°. (Lit.²⁵ m.p. 59°).

m-Chlorobenzyl alcohol

m-Chlorobenzyl alcohol (Aldrich) was distilled at 20 mm, the fraction boiling at 135-137° being collected.

Other substituted benzyl alcohols

The remaining substituted benzyl alcohols used were prepared by J.S. Ayers at the University of Canterbury. The liquid alcohols were redistilled and the solids used without further purification.

1-Methylcyclohexanol

Methyl magnesium iodide was prepared from methyl iodide (34.2g) and magnesium turnings (6g) in dry ether (130ml) and reacted slowly with cyclohexanone (21.6g) in dry ether (100ml) by the method of Helmkamp and Johnson²⁷. Distillation at 20 mm (b.p. 68-70°) gave 1-methylcyclohexanol, m.p. ca 25°. (Lit.²⁵ m.p. 25°).

1-Methylcyclohexyl acetate²⁸

Acetyl chloride (3.9g) was added to a stirred solution of 1-methylcyclohexanol (2.8g) in dimethylaniline (15ml) at 0° and the mixture allowed to stand at 20° for 1 hour, then heated on a steam bath for 4 hrs and, after cooling, poured into ice-water containing 10% HCl. Isolation via pentane followed by distillation at 20 mm gave the acetate, b.p. 76-77° (20 mm), n_D^{19} 1.4460. (Lit.²⁸ b.p. 74° @ 20 mm, n_D^{20} 1.4435).

Preparation of 5 α -hydroxysteroids (1)

To a solution of cholestane-3 β , 5 α -diol (5.8g) in pyridine (30ml) was added acetic anhydride (6ml) and the mixture allowed to stand for 3 days at 20°, then poured into water. Extraction with ether followed by removal of the solvent and recrystallisation from acetone gave 3 β -acetoxycholestan-5 α -ol (1c) (5.5g), m.p. 181-182°, $[\alpha]_D + 10^\circ$. (Lit.²¹ m.p. 185-185.5°, $[\alpha]_D + 12^\circ$).

A similar preparation using 6 β -methylcholestane-3 β , 5 α -diol gave 3 β -acetoxy-6 β -methylcholestan-5 α -ol (1d), m.p. 166-167 $^{\circ}$, (Lit.²¹ m.p. 164-165 $^{\circ}$).

3 β , 6 β -diacetoxycholestan-5 α -ol (1a)
3 β -acetoxy-6 β -methoxycholestan-5 α -ol (1b) and
3 β -acetoxy-6 β -chlorocholestan-5 α -ol (1c)
were prepared by other members of this department
and used without further purification.

Identification of Products from Reactions of (1c) and (1d)

3 β -acetoxy-6 β -methylcholestan-5 α -ol (1d)
(1000 mg) was treated with sulphuric acid (3×10^{-4} M)
and acetic anhydride (0.53M) in acetic acid for 17 mins
at 25 $^{\circ}$, then poured into water. Isolation via
ether gave a gum which was adsorbed onto 75g alumina.

Elution with light petroleum gave 3 β -acetoxy-6 β -
methylcholest-5-ene (5b) (810mg), m.p. 113-114 $^{\circ}$,
[α]_D - 52 $^{\circ}$ (dioxan). (Lit.^{21,29} m.p. 115-115.5 $^{\circ}$,
[α]_D -48 $^{\circ}$ (dioxan)).

Elution with benzene gave 3 β , 5 α -diacetox-
y-6 β -methylcholestane (2c) (152mg), shown by NMR and
IR to contain two acetate groups and no hydroxy group.

3 β -acetoxycholestan-5 α -ol (1c) was treated simil-
arly. Elution with light petroleum gave a mixture
of 3 β -acetoxycholest-5-ene (5a) and 3 β -acetoxycholest-
4-ene (4c) shown by NMR to consist of about 80% of (5a)
and 20% of (4c).

Experimental Procedure for Non-steroidal Alcohols

Stock solutions of sulphuric acid in acetic acid (0.05 and 0.01 molar) were prepared. A solution (35ml) of acetic anhydride and sulphuric acid in acetic acid and a solution (15ml) of the alcohol in acetic acid were prepared and placed in a thermostatted water bath at $25^{\circ} \pm 0.1^{\circ}$. Actual concentrations used for various runs are given in the results section. After temperature equilibrium had been attained (15-20 min) the two solutions were mixed. At suitable time intervals samples were withdrawn and added to a mixture of 0.880 ammonia (10ml), water (20ml) and ice (15g).

Methods of Analysis

Two methods of analysis were used for acyclic and monocyclic alcohols.

(a) Gas chromatographic analysis

This method was used for cyclohexanol. 5 ml samples of the reaction mixture were quenched and a suitable volume of a solution of mesitylene (used as an internal standard) in methanol (2% v/v.) added. The mixture was extracted three times with dichloromethane (25ml), the combined extracts dried (MgSO_4), the solvent removed by vacuum distillation and the residual liquid injected into a gas chromatograph (N_2 carrier, 15% silicone oil

on Chromosorb P, 125⁰, Gow-Mac gas density detector). The ratio of the amounts of acetate to standard present in a sample could be calculated using a correction factor for the chromatogram peak areas (measured by using a recorder incorporating a disc integrator) dependent on the molecular weights of the two compounds (see Calculation of Results).

(b) Infrared analysis

This method was used for the benzyl alcohols and methylcyclohexanol. 3 ml or 4 ml samples of the reaction mixture were taken and quenched and the acetate extracted three times with carbon tetrachloride. The combined extracts were dried (Na₂SO₄) and made up to 100 ml in volumetric flasks. The maximum absorbance of these solutions in the region 1740-1720 cm⁻¹ was measured on a Perkin Elmer model 221 or 421 spectrophotometer using a 5 mm cell with a similar cell containing carbon tetrachloride in the reference beam. Instrument settings used were as follows.

Instrument	421	221
Slit program	1000	927
Attenuator speed	1100	794
Amplifier gain	3.5	3.3

The volume of the sample taken from the mixture (3 or 4ml) was adjusted so as to bring the absorbance for complete reaction in the region 60-90% and the CCl_4 solutions were diluted by a known factor if necessary to bring the absorbance into this range.

Experimental Procedure for Steroidal Alcohols

Reactions were followed by measuring the change in optical rotation. Equal volumes (2ml) of acetic acid solutions of steroid, sulphuric acid and acetic anhydride, all at 25° , were mixed and the reaction mixture rapidly transferred into a 2 cm optical cell of a recording polarimeter (ETL-NPL Automatic Polarimeter type 143A, Bendix Electronics Ltd.) The optical unit was maintained at $25.0 \pm 0.2^\circ$ by means of an air thermostat. The optical rotation (Sodium D) was recorded continuously.

Calculation of Results.

(a) First order reactions

For reactions which are pseudo-first order, the rate constant, k_1 , can be evaluated from a plot of $\log (a-x)$ vs t , which has a slope of $-k/2.303$ where

a = initial concentration of alcohol

x = concentration of product at time t

(i) Gas chromatographic analysis

The measured variables are the peak areas of the product and standard. These areas are corrected by multiplication

by an area factor for each substance equal to $M_c/(M_c - M_g)$ where M_c is the molecular weight of the compound and M_g is the molecular weight of the carrier gas (nitrogen). So for mesitylene, M.W. 120, the area factor is 1.305. For cyclohexyl acetate, M.W. 142, the area factor is 1.246.

The ratio of the corrected areas is equal to the ratio of the weights of each compound in the sample and, since the weight of standard is known, the weight and thus the number of moles of acetate can be calculated.

The value of "a" is the stoichiometric concentration of alcohol.

(ii) Infrared analysis

The absorbance A_t of each sample is measured and used as x in the calculations; a is taken to be the value of the absorbance (A_∞) at the completion of the reaction since this is related to the original concentration of alcohol. The extinction coefficient need not be measured if there are no side products or if the ratio of side products to product measured remains constant during the reaction (see Discussion of Methods).

If these conditions hold, then

$$A_t = \epsilon c_t l \quad \text{and} \quad A_\infty = \epsilon c_\infty l$$

where l is the cell length and c_t and c_∞ are the concentrations of acetate at time t and the completion of reaction respectively.

$$\text{So } c_t = A_t/\epsilon l \quad \text{and} \quad c_\infty = A_\infty/\epsilon l$$

Then substituting these values in the rate equation

$$kt = \ln a - \ln (a - x).$$

$$\begin{aligned} kt &= \ln c_\infty - \ln (c_\infty - c_t) \\ &= \ln \frac{A_\infty}{\epsilon l} - \ln \left(\frac{A_\infty}{\epsilon l} - \frac{A_t}{\epsilon l} \right) \\ &= \ln A_\infty - \ln \epsilon l - \ln (A_\infty - A_t) + \ln \epsilon l \\ &= \ln (A_\infty - A_t) + \text{constant} \end{aligned}$$

So a plot of $\log (A_\infty - A_t)$ vs t has a slope of $-k/2.303$ and the extinction coefficient need not be measured.

(b) Zeroth-order reactions

For reactions which are pseudo-zero order in alcohol (p-anisyl alcohol, methylcyclohexanol, and the steroids at low sulphuric acid concentrations) the initial rate is measured directly. For methylcyclohexanol the extinction coefficient of the acetate product was measured and the amount of acetate present at time t calculated using this.

p-Anisyl alcohol was assumed to give only one product, the acetate, (Discussion of Methods) and so the dependence of the absorbance on the concentration of the acetate was assumed to remain constant up to complete reaction. The ratio of the absorbance, A_{∞} , at complete reaction to the original stoichiometric concentration of alcohol, c_s , (equal to the concentration of product at complete reaction) gives a measure of the dependence of absorbance on concentration in divisions per (mole/litre). The initial slope, k , of the plot of absorbance vs t is divided by this ratio to give the initial rate.

$$\text{Initial rate} = \frac{kc_s}{A_{\infty}}$$

A similar method of calculation of the initial rate was used for the steroids; the initial slope of the plot of optical rotation vs t was divided by the total rotation change to give a pseudo rate constant which was then multiplied by the stoichiometric concentration of alcohol used. The rates of reaction of steroids at higher acid concentrations were calculated by the Guggenheim³⁰ method.

Typical Kinetic Runs

The calculation of results for the three methods

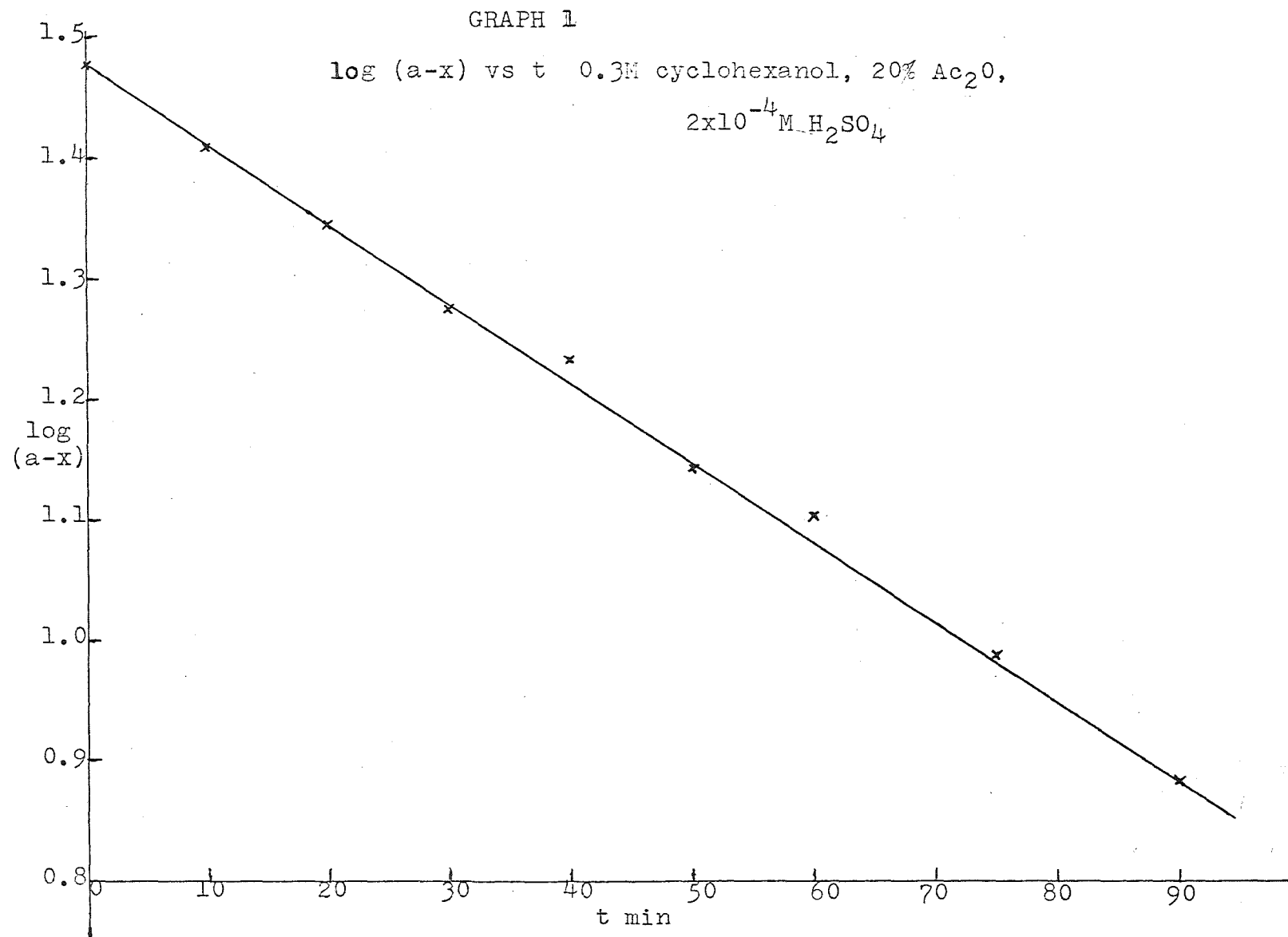
of analysis used is illustrated by the following typical runs.

(a) Gas chromatographic analysis

The reaction mixture contained 0.3M cyclohexanol and 2×10^{-4} M sulphuric acid in acetic anhydride - acetic acid (1:4) as solvent. 5 ml samples of the reaction mixture were quenched as previously described and 6 ml of the mesitylene solution added (103.8 mg per sample).

In the following table A_A is the area under the acetate peak and A_M the area under the mesitylene peak.

t min	A_A peak	corr.	A_M peak	corr.	area ratio	wt acetate mg/5 ml	10^2 [acetate] moles.l ⁻¹
10	43	54	139	181	0.298	30.9	4.35
20	41	51	73	95	0.537	55.7	7.84
30	128	159	159	208	0.764	79.3	11.17
40	111	138	120	156	0.885	91.9	12.94
50	213	265	184	240	1.104	114.6	16.14
60	161	201	130	170	1.182	122.7	17.28
75	227	283	156	204	1.387	144.0	20.28
90	297	370	185	242	1.529	158.7	22.34



x is equal to 10^2 [acetate] and $a = 10^2 c_s = 30$, $\log a = 1.477$

t min	x	$a-x$	$\log (a-x)$
10	4.35	25.65	1.409
20	7.84	22.16	1.345
30	11.17	18.83	1.275
40	12.94	17.06	1.232
50	16.14	13.86	1.142
60	17.28	12.72	1.104
75	20.28	19.72	0.988
90	22.34	7.66	0.884

The above results are plotted in Graph 1; the slope of $6.60 \times 10^{-3} \text{ min}^{-1}$ gives

$$k_1 = 2.54 \times 10^{-4} \text{ sec}^{-1}$$

$$\text{Initial rate} = 7.60 \times 10^{-5} \text{ moles l}^{-1} \text{ sec}^{-1}.$$

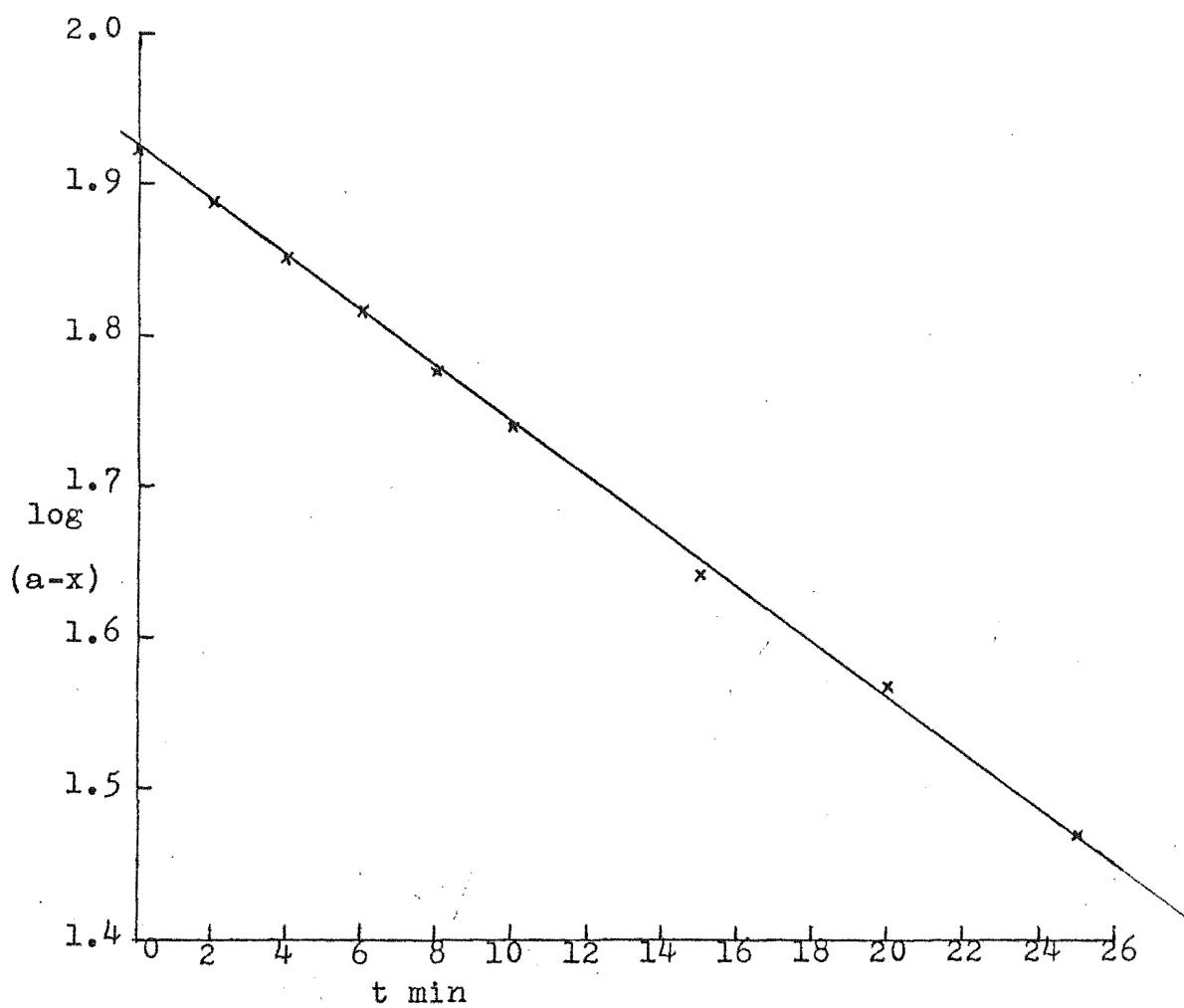
(b) Infrared analysis

The reaction of *p*-bromobenzyl alcohol with acetic anhydride and sulphuric acid in acetic acid at 25° .

Initial concentrations:

alcohol	0.1M
sulphuric acid	$2 \times 10^{-4} \text{ M}$
acetic anhydride.	20%

GRAPH 2

 $\log (a-x)$ vs t 0.1M p-bromobenzyl alcohol20% Ac_2O , 2×10^{-4} H_2SO_4 

The maximum absorbance was measured and a base height equal to the minimum absorbance in the region 1800-1780 cm^{-1} subtracted.

t mins	peak ht divs	base ht divs	net ht x divs	a-x	log (a-x)
2	7.4	1.1	6.3	77.3	1.888
4	14.1	1.4	12.7	70.9	1.851
6	19.4	1.3	18.1	65.5	1.816
8	25.3	1.4	23.9	59.7	1.776
10	30.1	1.5	28.6	55.0	1.740
15	42.0	2.2	39.8	43.8	1.642
20	48.7	2.1	46.6	37.0	1.568
25	56.6	3.5	54.1	29.5	1.470
4 hrs	86.4	2.9	83.5	average infinity point	
"	87.0	3.3	83.7	= a = 83.6.	

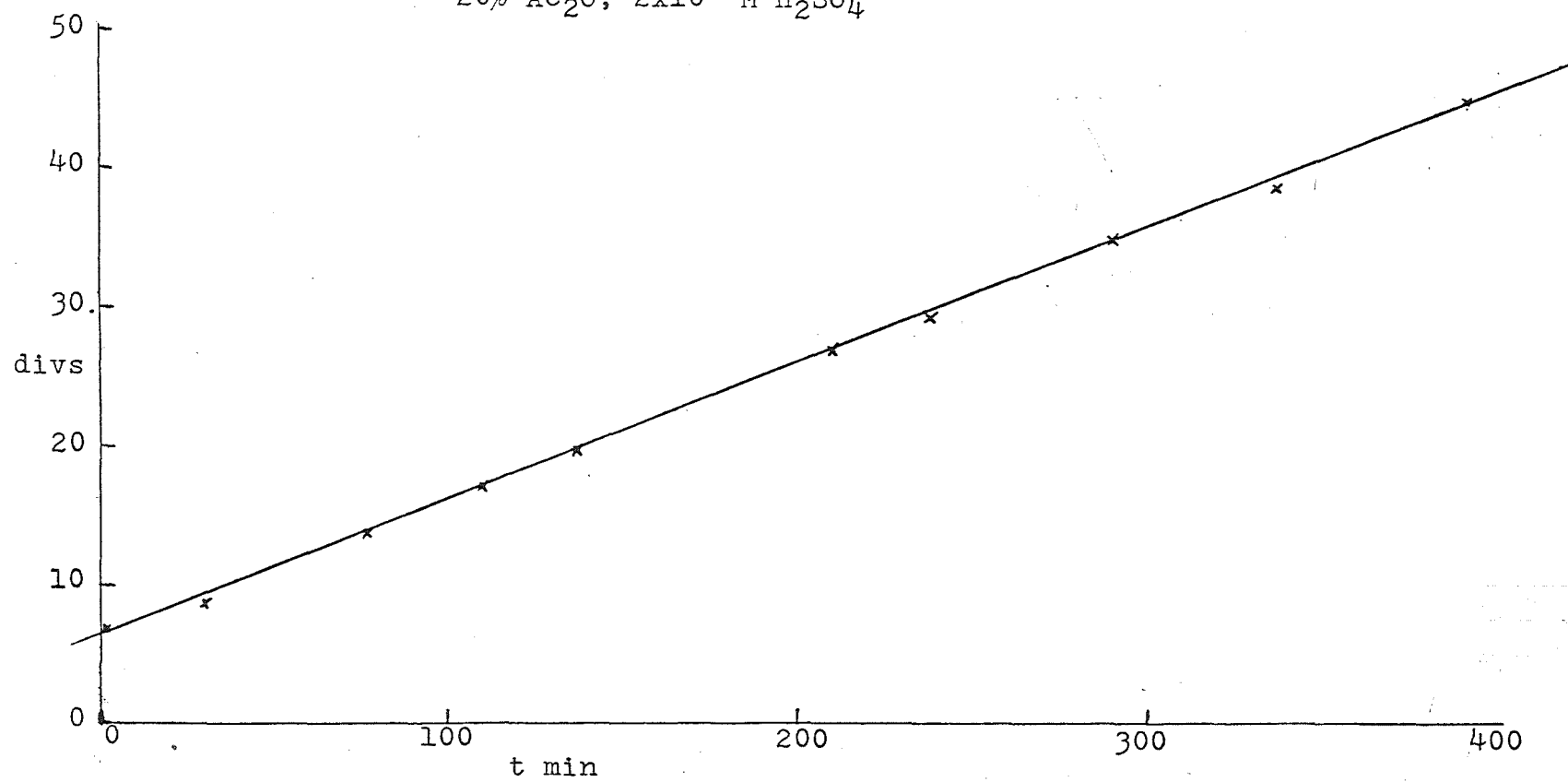
The above results are plotted in Graph 2; the slope of $1.81 \times 10^{-2} \text{ min}^{-1}$ gives

$$k_1 = 6.96 \times 10^{-4} \text{ sec}^{-1}$$

$$\text{Initial rate} = 6.96 \times 10^{-5} \text{ moles l}^{-1} \text{ sec}^{-1}.$$

GRAPH 3

optical rotation vs t

0.0105M 3 β ,6 β -diacetoxycholestan-5 α -ol20% Ac₂O, 2x10⁻⁴M H₂SO₄

(c) Polarimetric analysis

The reaction of 3 β , 6 β -diacetoxycholestan-5 α -ol (1a) with acetic anhydride-sulphuric acid in acetic acid at 25 $^{\circ}$.

Initial concentrations: steroid 0.1M
 sulphuric acid 2 x 10 $^{-4}$ M
 acetic anhydride 20%

The reading of the polarimeter recorder in divisions is plotted against time in Graph 3. The slope of 9.8 x 10 $^{-2}$ divisions per min was divided by the total change in rotation, 93.1 divs, to give a pseudo rate constant

$$k_p = 1.05 \times 10^{-3} \text{ min}^{-1}$$

$$\text{Initial rate} = 1.84 \times 10^{-7} \text{ moles l}^{-1} \text{ sec}^{-1}.$$

For the other steroids the initial slope was measured directly from the recorder chart; for the slow reaction of the 6 β -acetoxy compound this was not practicable.

Discussion of Kinetic Methods

Assumptions in calculations

In the calculation of results for reactions analysed by the infrared and polarimetric methods it was assumed that the reaction of an alcohol with sulphuric acid and acetic anhydride gave only one product or that all

products were present in the same proportions at any given time.

For the benzyl alcohol series it is difficult to see any product other than the acetate being formed since elimination of the benzyl cation is unknown. If elimination products were formed for any alcohol in constant ratio to the acetate then the method used would still be valid. The absorbance at time t and the absorbance at complete reaction would be changed by the same factor. The slope of a log plot would therefore not be affected and the initial rate of a zero order reaction could be calculated by multiplying the initial slope by the ratio of the stoichiometric concentration of alcohol at the start of the reaction to the absorbance at complete reaction (p 32). This would apply if the carbonium ion mechanism were the only significant mechanism; the reactions of steroids come into this category.

For 1-methylcyclohexanol there are two competing reactions, one first order in alcohol and the other zeroth-order; since the olefinic products are only produced by the latter reaction the proportion of these changes as the reaction proceeds. Therefore the extinction coefficient must be determined for methylcyclohexyl acetate.

Accuracy of results

The rates of reaction for all alcohols studied, except the steroids, were measured by determination of the concentration of acetate present in samples taken at known time intervals. The errors in these determinations are considered to be about $\pm 2-3\%$, made up of errors in the analytical method and in sampling. It is thought that the error was a little greater for cyclohexanol, where gas chromatographic analysis was used, than for those alcohols where infrared analysis was used. The scatter of points in the plots of $\log (a-x)$ vs t was found to be greater for cyclohexanol than for the other alcohols. This scatter leads to a possible variation in the slope of the plot, estimated to be about $\pm 2\%$.

In addition to this variation, there is a possible error in the rate caused by inaccuracies in the concentrations of reagents in the reaction mixture and (for infrared analysis) the determination of the infinity point. These errors bring the overall accuracy of the rate to about $\pm 5\%$. In most cases reproducibility checks were not carried out but the rates were measured at different concentrations and plotted against the concentrations of reactants. The results were found to fit the expected linear relationships well, the variation of each point from the best straight line being

less than 5% in most cases. The effect of 5% or 10% variations in the rates are shown for some points on Graphs 4 - 13 as dotted arrows.

The rates of reaction of steroid alcohols were measured by a method different from those above and the errors appeared to be greater. Most of the rates were calculated by measuring the initial slope of the plot of optical rotation vs time. The 6 β -methyl and 6-deoxy compounds reacted very rapidly, the half life being less than 5 mins. The slopes of the plots were therefore large and less easy to measure accurately. In addition the overall rotation change for these steroids was only small. The expansion device used to convert the polarimeter reading to a reading on the recorder had therefore to be at a high setting which greatly magnified small fluctuations in the optical rotation. Even the rates for the 6 β -acetoxy compound were not as reproducible as expected at low sulphuric acid concentrations. For this compound the rotation change is large and the rate of change low so that the rates should be more reproducible than for the other alcohols. It did appear that the reactions of steroids with acetic anhydride and sulphuric acid

at low concentrations of the latter were more sensitive to traces of impurities than those of other alcohols. In addition, side products were produced in some of the reactions of steroids. The contribution of these to the optical rotation was small¹⁴ but if the ratio of the amounts of the various products was not constant throughout the reaction then large errors would be introduced.

It is considered therefore that the quoted rates for steroids are not accurate to any better than $\pm 20\%$ and the variation between runs under the same conditions was often greater than this. However since the rates for different steroids differ by factors much greater than 1.2, comparisons of these rates are significant.

During the course of this work it was necessary to use different batches of solvents for the reactions. The same batch of solvent was used for all the reactions of a given compound but changes of solvent could affect the relative rates of different compounds. This was allowed for by measuring the rate of reaction of a previously studied compound in the new solvent (see Table VIII). However the change of solvent, although corrected for to some extent, must be a source of additional error in the relative rates of benzyl alcohols and may account, in part, for the scatter of these rates.

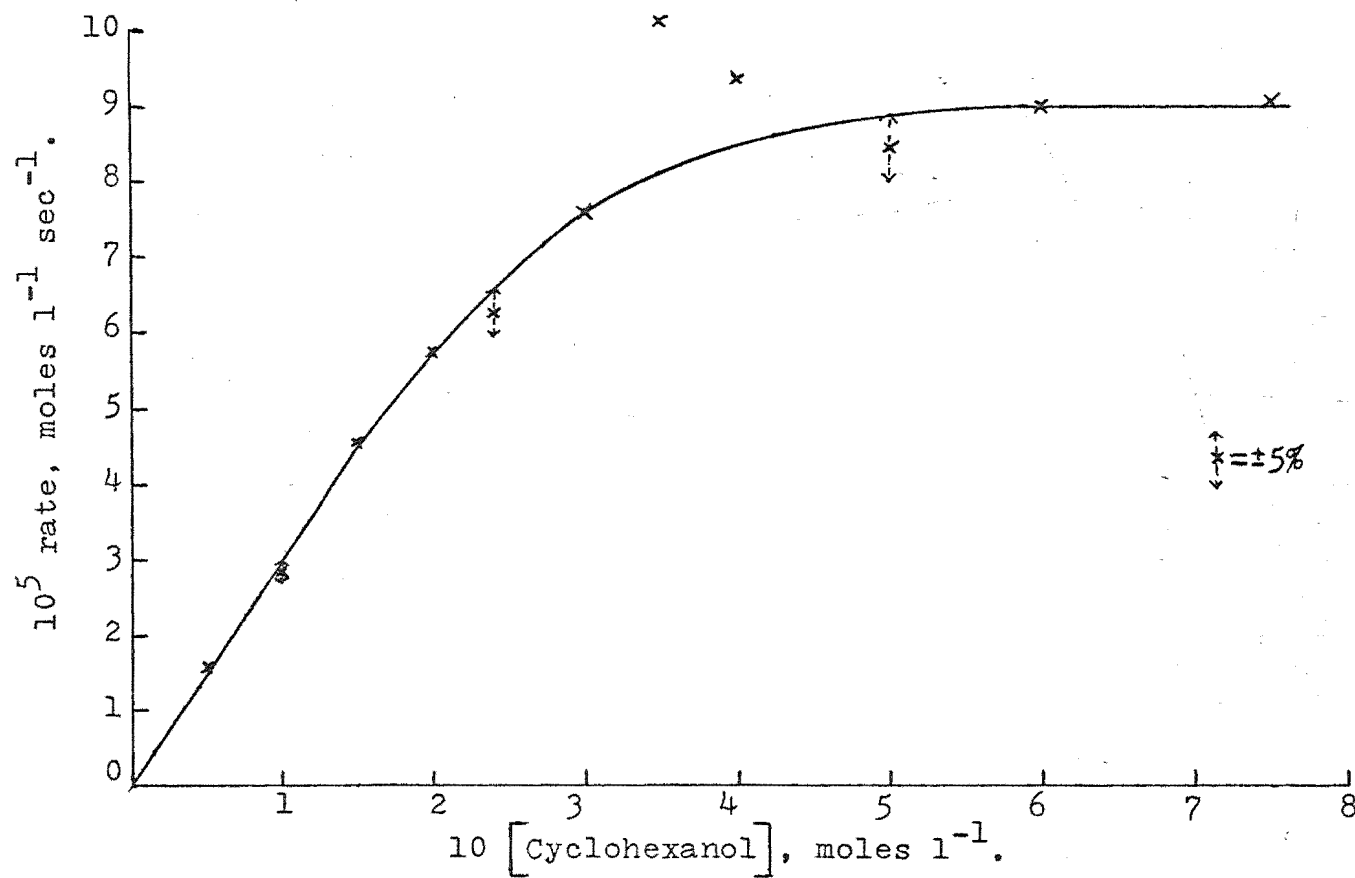
KINETIC RESULTS

Table I - Cyclohexanol

No.	[cyclohexanol]	$10^4 [\text{H}_2\text{SO}_4]$	$[\text{Ac}_2\text{O}]$	$10^5 \text{ Rate moles l}^{-1} \text{ sec}^{-1}$
1	0.1	1	0.53	0.23
2	0.1	10	0.53	2.83
3	0.1	30	0.53	8.18
4	0.1	50	0.53	10.9
5	0.1	70	0.53	17.6
6	0.1	100	0.53	24.2
7	0.05	2	2.12	1.59
8	0.1	2	2.12	2.85
9	0.15	2	2.12	4.55
10	0.2	2	2.12	5.73
11	0.24	2	2.12	6.26
12	0.3	2	2.12	7.60
13	0.35	2	2.12	10.12
14	0.4	2	2.12	9.35
15	0.5	2	2.12	8.45
16	0.6	2	2.12	8.99
17	0.75	2	2.12	9.07
18	1.0	2	2.12	6.99
19	0.1	10	1.06	5.64
20	0.1	10	2.12	12.6
21	0.4	2	1.06	3.12
22	0.4	2	1.59	6.68

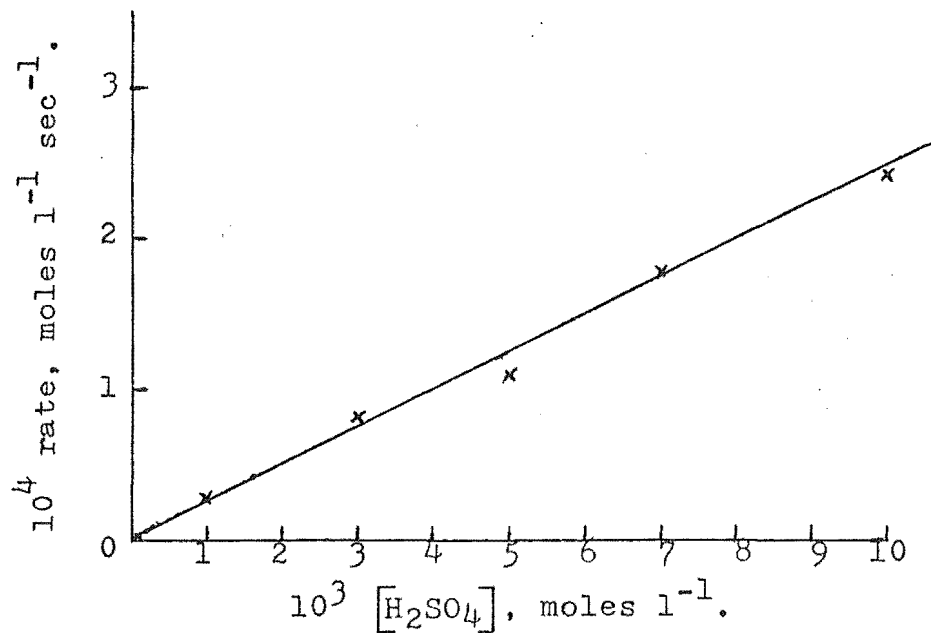
GRAPH 4

Rate plot for reaction of cyclohexanol with

 $2 \times 10^{-4} \text{ M H}_2\text{SO}_4$ and $2.12 \text{ M Ac}_2\text{O}$ 

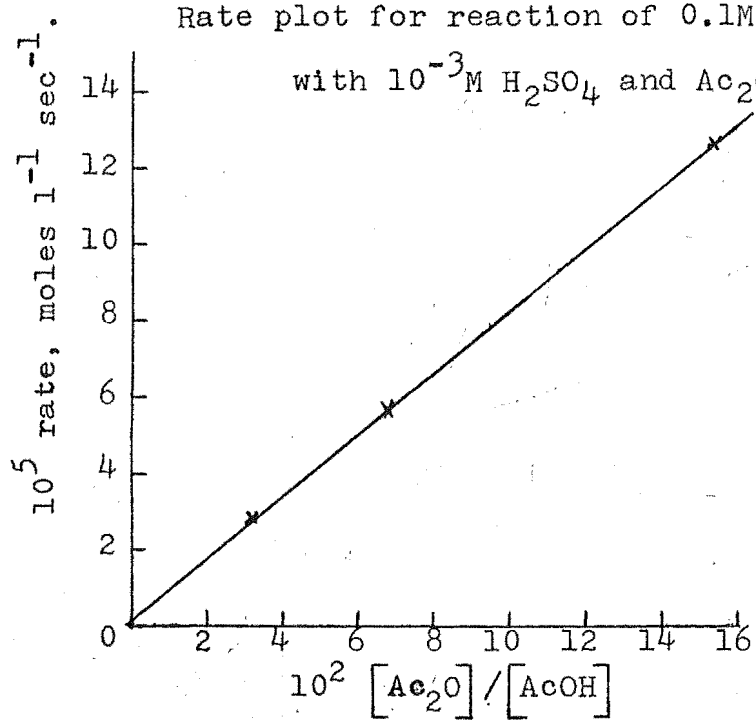
GRAPH 5

Rate plot for reaction of 0.1M cyclohexanol
with H_2SO_4 and 0.53M Ac_2O



GRAPH 6

Rate plot for reaction of 0.1M cyclohexanol
with $10^{-3} \text{M } \text{H}_2\text{SO}_4$ and Ac_2O



Cyclohexanol

Initial rates for the reactions of cyclohexanol with sulphuric acid-acetic anhydride in acetic acid at 25° are given in Table I. The rates for runs 1 - 6 are plotted against $[H_2SO_4]$ in Graph 5. The rates for runs 7 - 18 are plotted against $[cyclohexanol]$ in Graph 4. The rates for runs 14, 19 and 20 are plotted against $[Ac_2O] / [AcOH]$ in Graph 6.

From Graph 5 the value of the rate constant k_1 at 20% acetic anhydride and $2 \times 10^{-4}M$ sulphuric acid is $2.88 \times 10^{-4} \text{ sec}^{-1}$. The rate of acetylation of cyclohexanol was also measured using infrared analysis; k_1 was found to be 2.54 (a year later).

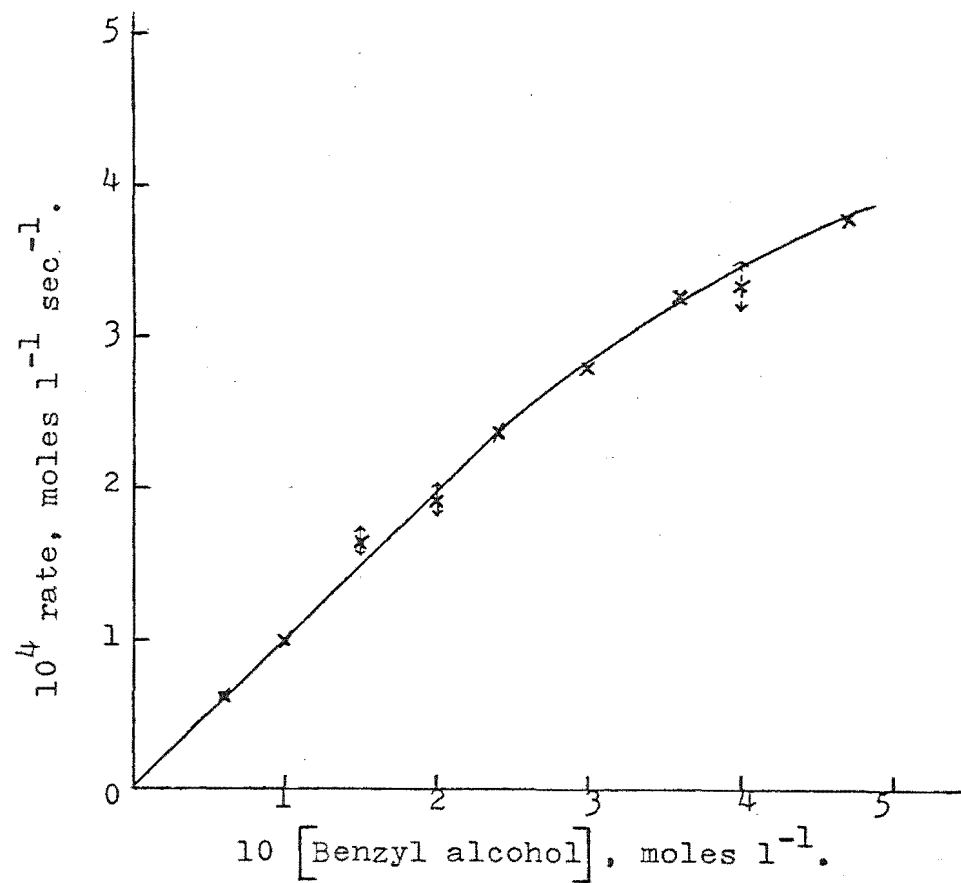
units sec^{-1}

Benzyl alcohol

Initial rates for reactions of benzyl alcohol with sulphuric acid-acetic anhydride in acetic acid at 25° are given in Table II. The rates for runs 1 - 9 are plotted against $[alcohol]$ in Graph 7. The rates for runs 2, 10, 11 and 12 are plotted against $[Ac_2O] / [AcOH]$ in Graph 8 and the rates for runs 12 - 21 are plotted against $[H_2SO_4]$ in Graph 9. The rate constant k_1 at 20% acetic anhydride and $2 \times 10^{-4}M$ sulphuric acid is taken from Graph 7 to be $9.75 \times 10^{-4} \text{ sec}^{-1}$.

GRAPH 7

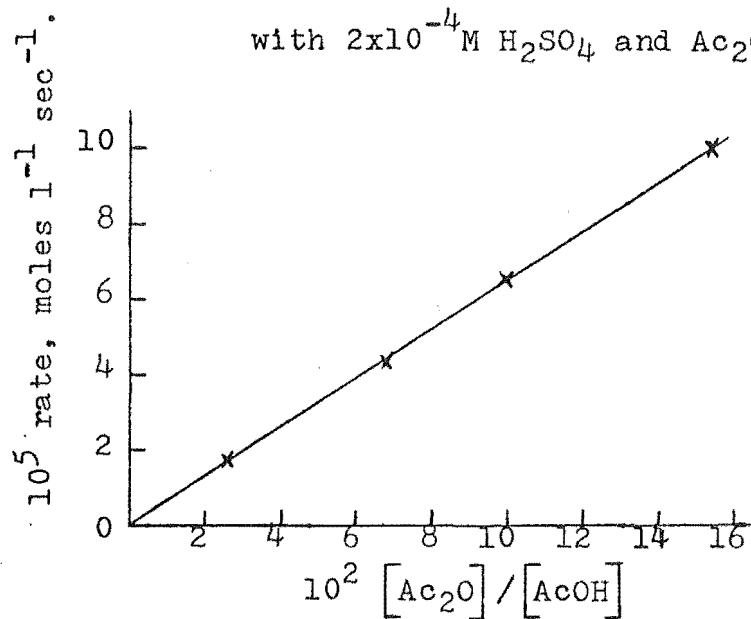
Rate plot for reaction of benzyl alcohol with
 $2 \times 10^{-4} \text{ M H}_2\text{SO}_4$ and $2.12 \text{ M Ac}_2\text{O}$



$\hat{*} = \pm 5\%$

GRAPH 8

Rate plot for reaction of 0.1M benzyl alcohol
with 2×10^{-4} M H_2SO_4 and Ac_2O



GRAPH 9

Rate plot for reaction of 0.1M benzyl alcohol
with H_2SO_4 and 0.42M Ac_2O

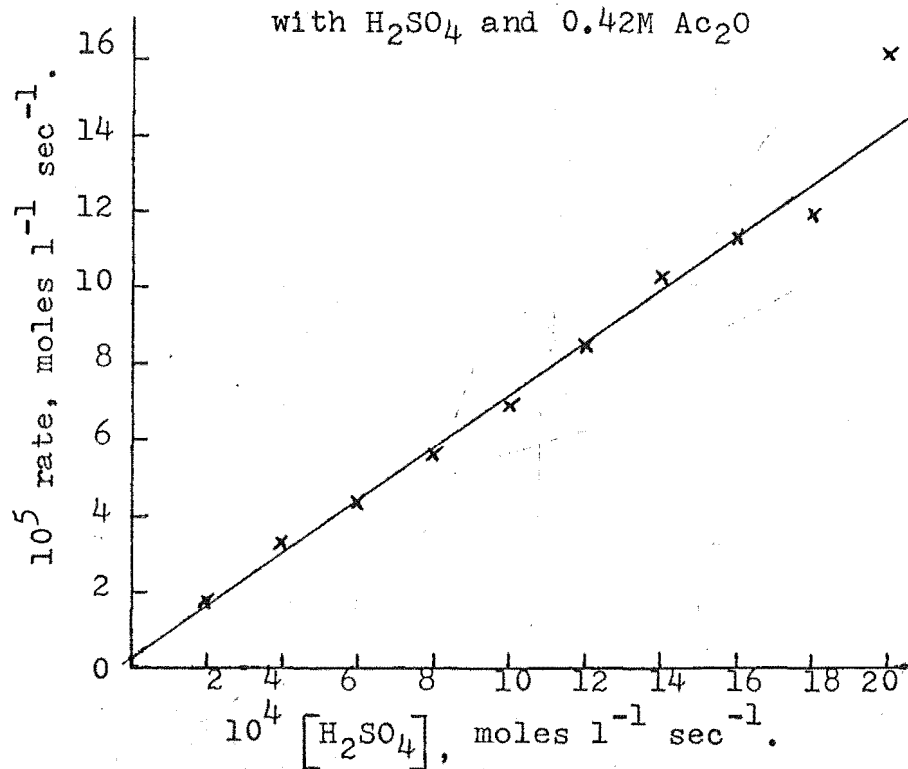


Table II - Benzyl alcohol

No.	[alcohol]	10^4 $[H_2SO_4]$	$[Ac_2O]$	10^5 Rate moles $l^{-1} sec^{-1}$.
1	0.06	2	2.12	6.33
2	0.1	2	2.12	9.94
3	0.15	2	2.12	16.4
4	0.2	2	2.12	19.2
5	0.24	2	2.12	23.7
6	0.3	2	2.12	27.9
7	0.36	2	2.12	32.6
8	0.4	2	2.12	33.4
9	0.47	2	2.12	37.8
10	0.1	2	1.48	6.54
11	0.1	2	1.06	4.34
12	0.1	2	0.42	1.78
13	0.1	4	0.42	3.32
14	0.1	6	0.42	4.35
15	0.1	8	0.42	5.60
16	0.1	10	0.42	6.88
17	0.1	12	0.42	8.44
18	0.1	14	0.42	10.3
19	0.1	16	0.42	11.3
20	0.1	18	0.42	11.9
21	0.1	20	0.42	16.1

p-Anisyl alcohol

Initial rates for the reaction of p-anisyl alcohol with sulphuric acid ($2 \times 10^{-4}M$) and acetic anhydride (2%) in acetic acid at 25° are given below.

TABLE III

[alcohol]	10^5 Rate moles l^{-1} sec^{-1}
0.1	7.45
0.2	6.92

The mean rate is 7.18×10^{-5} moles l^{-1} sec^{-1}

p-Nitrobenzyl alcohol

Initial rates for the reaction of p-nitrobenzyl alcohol with sulphuric acid-acetic anhydride in acetic acid at 25° are given below.

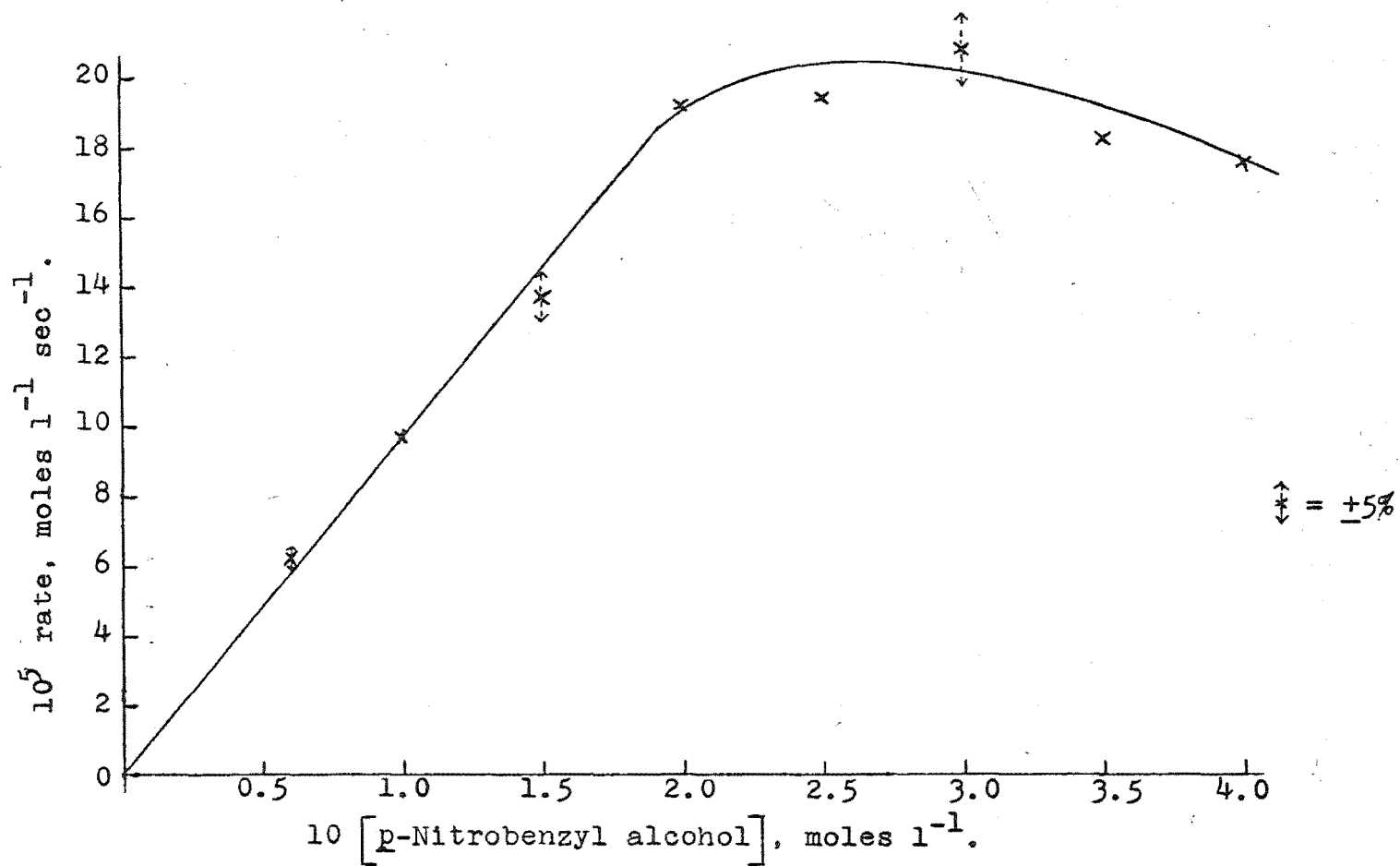
TABLE IV

No.	[alcohol]	$10^4 [H_2SO_4]$	$[Ac_2O]$	10^5 Rate moles $l^{-1} sec^{-1}$
1	0.06	2	2.12	6.25
2	0.1	2	2.12	9.68
3	0.15	2	2.12	13.7
4	0.2	2	2.12	19.2
5	0.25	2	2.12	19.4
6	0.3	2	2.12	20.8
7	0.35	2	2.12	18.2
8	0.4	2	2.12	17.5
9	0.1	2	1.06	4.28
10	0.1	2	0.42	1.62
11	0.1	6	0.42	5.76
12	0.1	10	0.42	9.92

The rates for runs 1 - 8 are plotted against [alcohol] in Graph 10; the mean value of k_1 at 20% acetic anhydride and $2 \times 10^{-4}M$ sulphuric acid is $9.62 \times 10^{-4} sec^{-1}$.

GRAPH 10

Rate plot for the reaction of p-nitrobenzyl alcohol
with 2×10^{-4} M H_2SO_4 and 2.12M Ac_2O



p-Methylbenzyl alcohol

Initial rates for the reaction of p-methylbenzyl alcohol with sulphuric acid ($2 \times 10^{-4}M$) and acetic anhydride (20%) in acetic acid at 25° are given below.

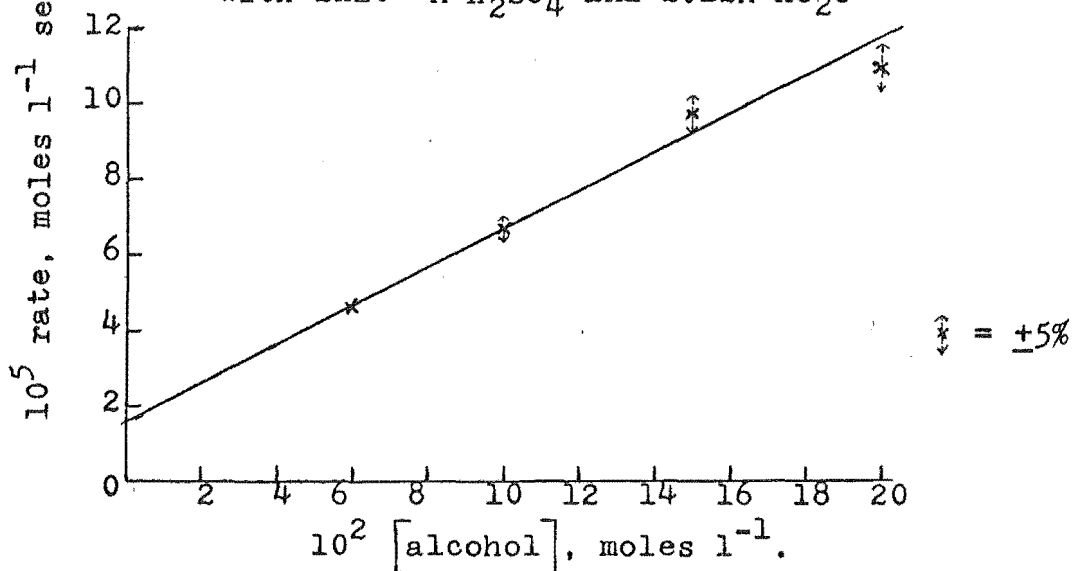
TABLE V

[alcohol]	10^5 Rate moles $l^{-1} \text{ sec}^{-1}$
0.06	4.61
0.1	6.64
0.15	9.73
0.2	10.9

The above results are plotted in Graph II. The intercept at $[\text{alcohol}] = 0$ is 1.57×10^{-5} moles $l^{-1} \text{ sec}^{-1}$ and the slope, k_1 is $5.07 \times 10^{-4} \text{ sec}^{-1}$, the former being the carbonium ion (zeroth-order) component of the rate and the latter the first order component.

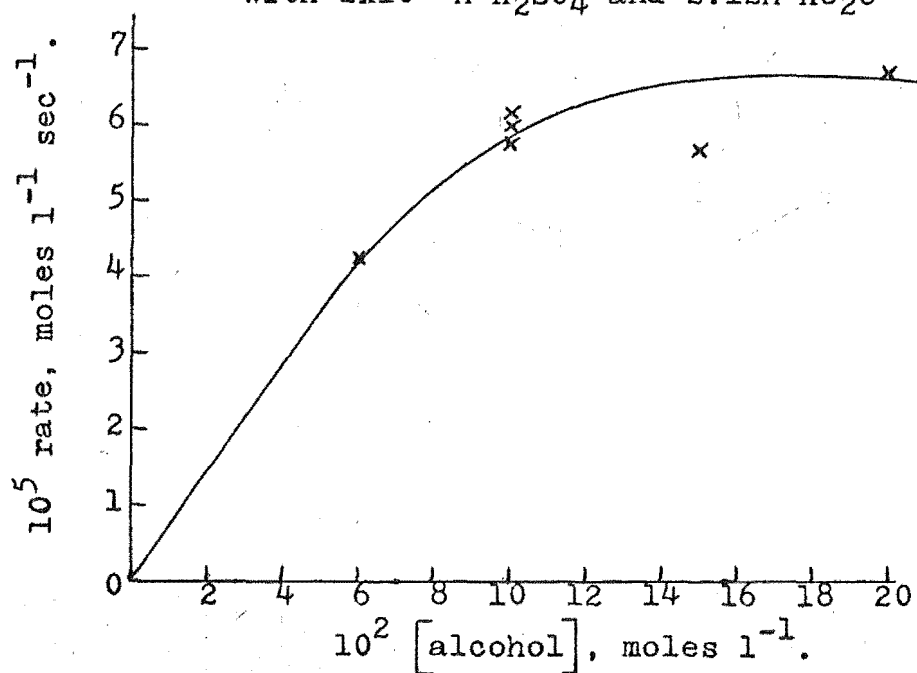
GRAPH 11

Rate plot for reaction of p-methylbenzyl alcohol
with 2×10^{-4} M H_2SO_4 and 2.12M Ac_2O



GRAPH 12

Rate plot for reaction of m-chlorobenzyl alcohol
with 2×10^{-4} M H_2SO_4 and 2.12M Ac_2O



m-Chlorobenzyl alcohol

Initial rates for the reaction of m-chlorobenzyl alcohol with sulphuric acid ($2 \times 10^{-4}M$) and acetic anhydride (20%) in acetic acid at 25° are given below.

TABLE VI

[alcohol]	10^5 Rate moles l^{-1} sec^{-1}
0.06	4.22
0.1	5.72
0.1	5.97
0.1	6.16
0.15	5.64
0.2	6.68

The above results are plotted in Graph 12. The slope of the linear part of the plot is $7.04 \times 10^{-4} sec^{-1}$.

Other substituted alcohols

Rate data for the reaction of various other substituted benzyl alcohols with sulphuric acid ($2 \times 10^{-4}M$) and acetic anhydride (20%) in acetic acid at 25° are given below.

TABLE VII

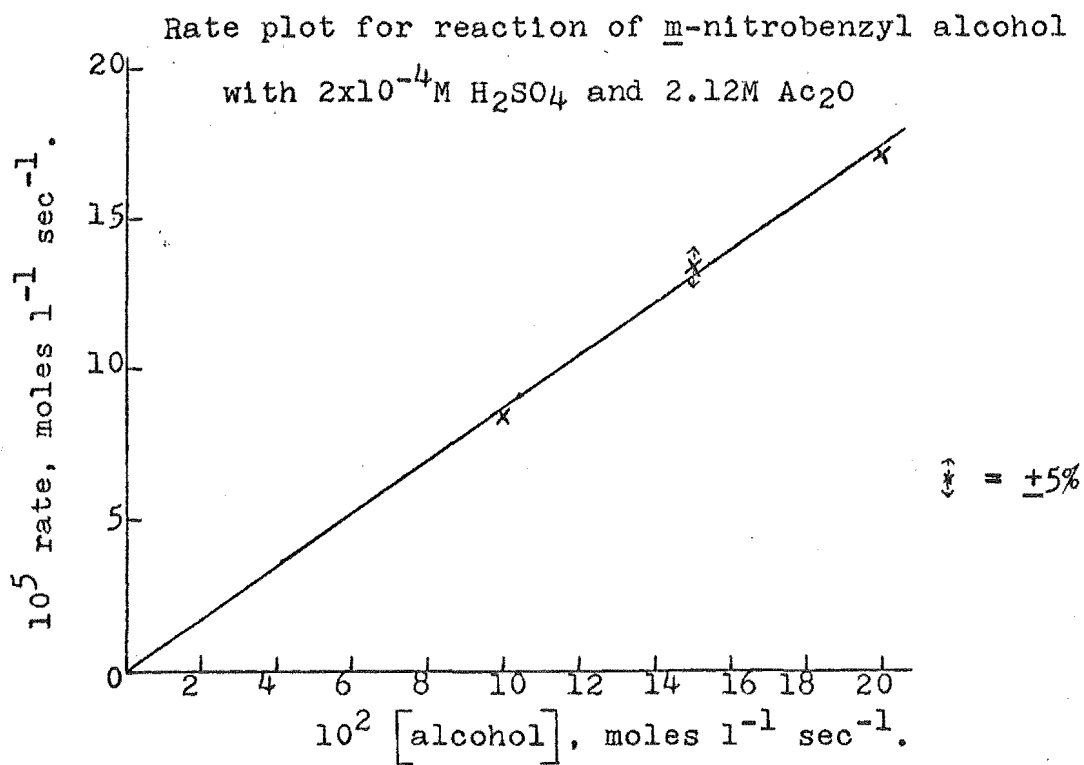
substituent	[alcohol]	10^5 Rate moles $l^{-1} \text{ sec}^{-1}$.
<u>m</u> -NO ₂	0.1	8.47
<u>m</u> -NO ₂	0.15	13.38
<u>m</u> -NO ₂	0.2	17.12
<u>p</u> -Br	0.1	6.96
<u>p</u> -Br	0.15	9.02
<u>p</u> -Br	0.181	12.23
<u>p</u> -Cl	0.1	7.64
<u>p</u> -Cl	0.15	11.03
<u>p</u> -Cl	0.2	16.20
<u>m</u> -Me	0.1	6.67
<u>m</u> -Me	0.1	6.75

TABLE VII (continued)

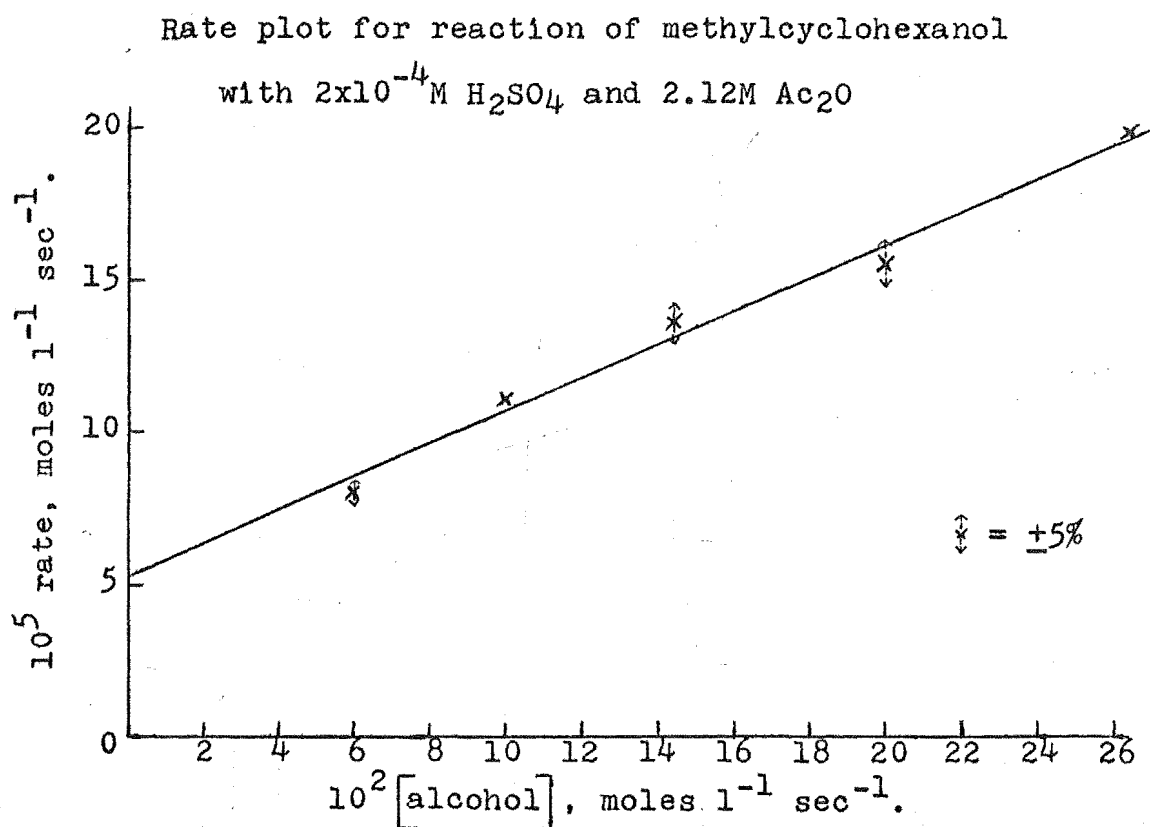
substituent	[alcohol]	10^5 Rate moles l^{-1} sec $^{-1}$
<u>m</u> -MeO	0.1	7.64
<u>m</u> MeO	0.1	8.22
<u>m</u> -MeO	0.15	11.29
<u>m</u> -MeO	0.2	16.06
<u>m</u> -Br	0.1	9.98
<u>m</u> -Br	0.1	10.3
<u>m</u> -Br	0.15	14.4
<u>m</u> -Br	0.2	20.5

For each compound the rates were plotted against alcohol and the plots found to pass through the origin. Values of k_1 were determined from the slope of the plot. An example is shown in Graph 13 where the rate is plotted against [m-nitrobenzyl alcohol].

GRAPH 13



GRAPH 14



The k_1 values obtained for the benzyl alcohols were corrected for change in reagent lots by comparison with further runs for previously measured compounds. For instance the rates for all compounds studied after *p*-nitrobenzyl alcohol were corrected for change in rate for this alcohol when a new stock sample of acetic anhydride was used. A summary of the rates of the reactions of various alcohols with different batches of reagents is given in Table VIII.

Table VIII

substituent	Ac ₂ O batch	AcOH batch	[Ac ₂ O]	10 ⁴ k ₁ sec ⁻¹
H	1	1	0.21	0.84
<i>p</i> -OMe	1	1	0.21	7.18
H	1	1	2.12	9.75
H	1	2	2.12	8.91
<i>p</i> -NO ₂	1	2	2.12	9.62
<i>p</i> -NO ₂	2	2	2.12	6.38
other subs.	2	2	2.12	-
H	2	3	2.12	8.82
<i>m</i> -Br	2	3	2.12	10.1

Relative rates for benzyl alcohols

The corrected values of k_1 for the various substituents were used to obtain the relative rates, given below.

TABLE IX

substituent	relative rate	remarks
H	1	
p-OMe	8.6	
p-NO ₂	1.08	
m-NO ₂	1.46	
p-Cl	1.31	
m-Cl	1.19	from linear part of plot
p-Me	1.12	from overall rate at 0.1M
m-Me	0.86	first order component.
m-Me	1.13	
m-OMe	1.34	
p-Br	1.10	
m-Br	1.15	

The Hammett ρ value for this reaction is very small, estimated to be about +0.2.

1-Methylcyclohexanol

The extinction coefficient for methylcyclohexyl acetate was 544 and this value was used to obtain the amount of acetate in each sample and hence the rates of formation of acetate, given below. These rates are less than the total rate of disappearance of alcohol because of the formation of by-products.

TABLE X

No.	[alcohol]	$10^4 [\text{H}_2\text{SO}_4]$	$[\text{Ac}_2\text{O}]$	$10^5 \text{ Rate moles l}^{-1} \text{ sec}^{-1}$
1	0.06	2	2.12	0.81
2	0.1	2	2.12	1.10
3	0.144	2	2.12	1.36
4	0.2	2	2.12	1.55
5	0.264	2	2.12	1.98
6	0.1	2	1.06	0.61
7	0.1	2	0.42	0.33

The rates for runs 1 - 5 are plotted against [alcohol] in Graph 14. The intercept at [alcohol] = 0 is 5.2×10^{-6} moles $\text{l}^{-1} \text{ sec}^{-1}$ and the slope is $5.45 \times 10^{-5} \text{ sec}^{-1}$.

Steroids

Rate data for reactions of various 6 β -substituted(X)-3 β -acetoxycholestan-5 α -ols (1) with sulphuric acid-acetic anhydride in acetic acid at 25 $^{\circ}$ are given below.

TABLE XI

X	$10^4 [\text{H}_2\text{SO}_4]$ moles l^{-1}	$[\text{Ac}_2\text{O}]$ m. l^{-1}	10^7 Initial rate m. l^{-1} sec $^{-1}$	10^7 mean rate m. l^{-1} sec $^{-1}$	Re- lat- ive rate, k_{rel}
AcO	2	2.12	2.6, 2.6, 2.7 1.8, 1.8, 1.7	2.2	1
MeO	2	2.12	70	70	32
H	2	2.12	430, 240, 360 300, 300	330	150
H	2	1.06	117, 97	107	150
Me	2	1.06	230, 244, 169	220	310
AcO*	167	0.42	10.8 10.3	10.6	1
Cl*	167	0.42	43.6 47.2	45.4	4.3

* $[\text{X}] = 0.01\text{M}$, this is the rate determining concentration,
not $[\text{H}_2\text{SO}_4]$ as for the other reactions above.

MASS SPECTROMETRIC STUDIES USING O¹⁸

The acetylation of an alcohol with sulphuric acid-acetic anhydride can proceed either by acyl-oxygen fission, incorporating one oxygen atom from the solvent into the acetate produced, or by alkyl-oxygen fission, incorporating two oxygen atoms. If the alcohol is treated with sulphuric acid in acetic anhydride-acetic acid enriched in O¹⁸, the number of oxygen atoms in the product so enriched (equal to the number incorporated from the solvent) can be determined.

EXPERIMENTAL AND RESULTS

Preparation of Solvent

Enriched water (YEDA, 60% enrichment, 1ml) was added to acetic anhydride (5.7ml) and the mixture heated on a steam bath with a reflux condenser and drying tube (CaCl₂) for 3½ hrs. Acetic anhydride (4.5ml) was added and the mixture heated at 100° for a further 3 hrs. Acetic acid (10.2ml) was added to dilute the acetic anhydride-acetic acid mixture to the required concentration and enrichment. The NMR spectrum of the mixture was found to be identical to that of a 1:4 acetic anhydride-acetic acid mixture. Addition of one drop of water to the latter caused a shift of 2 ppm in the acid proton resonance of acetic acid so the enriched sample was considered to be water-free.

Experimental Procedure

The alcohol (ca 130mg) was reacted for approximately six half-lives with sulphuric acid ($10^{-3}M$) in enriched acetic anhydride-acetic acid (1:4), 5ml being used for the steroids and 2ml for the other alcohols. The product was poured into ice-water-ammonia and extracted with ether. The extract was washed with $NaHCO_3$ solution, dried (Na_2SO_4) and the solvent removed under vacuum, yielding the acetate. A sample of each alcohol was also treated with unenriched acetic anhydride-acetic acid. Both products were sent for mass spectrometric analysis carried out by Dr A. Fischer at the University of Sussex on an A.E.I. MS9 instrument. The full spectrum of each sample was run and then a small region of the spectrum containing the parent peak, mass M , and the peaks of mass $M + 1$ and $M + 2$ repeated several times.

Calculation of Results

The mass spectra of 1-methylcyclohexyl acetate, cholestane-3 β ,5 α ,6 β -triol triacetate, and 6-ketcholestane-3 β ,5 α -diol diacetate were found to contain no parent peak so no calculations could be carried out. For the remaining compounds the heights, P , of the peaks of mass M , $M + 1$, $M + 2$ were measured and the ratios P_{M+1}/P_M , P_{M+2}/P_M and P_{M+2}/P_{M+1} calculated for each repetition of the spectrum and averaged for each compound.

It can be shown³¹ that for a compound $C_w H_x O_z$

$$\frac{P_{M+1}}{P_M} = 1.08 \times 10^{-2} w + 1.6 \times 10^{-4} x \quad (1)$$

$$\frac{P_{M+2}}{P_M} = 2.00 \times 10^{-3} z + 0.584 \times 10^{-4} w(w-1) \quad (2)$$

$$\frac{P_{M+2}}{P_{M+1}} = \frac{2.00 \times 10^{-3} z + 0.584 \times 10^{-4} w(w-1)}{1.08 \times 10^{-2} w + 1.6 \times 10^{-4} x} \quad (3)$$

In each case the additional terms quoted by Beynon³¹ make only a small contribution to the total except for compounds of high mass.

For the unenriched acetates the theoretical values of these ratios can be calculated from the above equations or obtained from tables³² and compared with the values obtained from the spectra. For the enriched acetates the value of P_{M+1}/P_M should be the same as that for the unenriched compound while the values of P_{M+2}/P_M and P_{M+2}/P_{M+1} should be greater.

In the O^{18} enriched ester, $C_w H_x O_{z-n} O'_n$, certain oxygen atoms, designated O' have been artificially enriched and the ratio of the number of O' atoms of mass 18 to the number of O atoms of mass 16 is taken as r . Then in the equations (2) and (3) above z is replaced by $z-n$ and an additional term, nr , is added to include the probability of an O' atom contributing to a mass of $M+2$. These equations then become:

$$\frac{P_{M+2}}{P_M} = nr + 2.00 \times 10^{-3}(z-n) + 0.584 \times 10^{-4}w(w-1)$$

$$\frac{P_{M+2}}{P_{M+1}} = \frac{nr + 2.00 \times 10^{-3}(z-n) + 0.584 \times 10^{-4}w(w-1)}{1.08 \times 10^{-2}w + 1.6 \times 10^{-4}x}$$

From these equations r can be calculated if n is known or n can be calculated if r is known.

Results

Cholestanyl acetate, $C_{29}H_{50}O_2$

The theoretical values for the unenriched ester and the mean experimental values for the unenriched and enriched esters are given below.

Ratio	Theoretical value ^{32b}	Experimental values	
		Unenriched	Enriched
P_{M+1}/P_M	0.322	0.30	0.32
P_{M+2}/P_M	0.0542	0.051	0.084
P_{M+2}/P_{M+1}	0.169	0.169	0.27

It is assumed that cholestanol incorporates only one oxygen from the solvent and therefore that n is 1; this is reasonable since the product analysis (p.17) indicates acyl-oxygen fission. A comparison with the other alcohols justifies this assumption. Then:

$$P_{M+2}/P = 0.084 = r + 0.002 + 0.047$$

$$\text{i.e. } r = 0.035$$

$$P_{M+2}/P_{M+1} = 0.27 = (r + 0.02 + 0.047)/0.322$$

$$\text{i.e. } r = 0.038$$

The average value of r from the above is 0.0365, equivalent to 3.8% enrichment. The solvent was prepared to be about 4% enriched so it appears reasonable to take $n=1$ for this alcohol.

Benzyl acetate, C₉H₁₀O₂

The theoretical and mean experimental values of the abundance ratios are given below.

Ratio	Theoretical value ^{32a}	Experimental values	
		Unenriched	Enriched
P _{M+1} /P _M	0.0996	0.097	0.101
P _{M+2} /P _M	0.00844	0.0077	0.045
P _{M+2} /P _{M+1}	0.0847	0.080	0.44

Taking $r = 0.0365$, n can be calculated as follows:

$$P_{M+2}/P_M = 0.045 = 0.0365n + 0.002(2-n) + 0.0042$$

$$\text{i.e. } n = 1.06$$

$$P_{M+2}/P_{M+1} = 0.44 = (0.0365n + 0.002(2-n) + 0.0042)/0.0996$$

$$\text{i.e. } n = 1.03$$

The average value of n is 1.05. Benzyl alcohol incorporates as many oxygen atoms from the solvent as cholestanol.

p-Anisyl acetate, C₁₀H₁₂O₃

The theoretical and mean experimental abundance ratios are given below.

Ratio	Theoretical value ^{32a}	Experimental values	
		Unenriched	Enriched
P _{M+1} /P _M	0.111	0.111	0.114
P _{M+2} /P _M	0.0116	0.0114	0.079
P _{M+2} /P _{M+1}	0.104	0.102	0.69

Taking $r = 0.0365$, then:

$$P_{M+2}/P_M = 0.079 = 0.0365n + 0.002(3-n) + 0.0053$$

$$\text{i.e. } n = 1.96$$

$$P_{M+2}/P_{M+1} = 0.69 = (0.0365n + 0.002(3-n) + 0.0053)/0.111$$

$$\text{i.e. } n = 1.89$$

The average value of n is 1.93. p-Anisyl alcohol incorporates almost twice as many oxygen atoms from the solvent as benzyl alcohol and β -cholestanol.

DISCUSSION

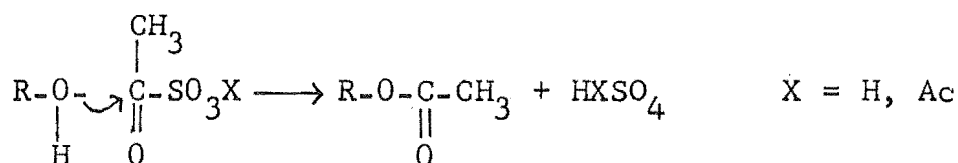
Reaction of 3 β -Cholesterol with Sulphuric acid-Acetic anhydride

The first reaction studied was the acetylation of 3 β -cholesterol (6a) with acetic anhydride and sulphuric acid, which could proceed by either of two mechanisms. Alkyl-oxygen fission of an acetyl sulphate ester could occur or the reaction could proceed through attack of the acyl function of the acetylating agent on the hydroxyl group of the alcohol (acyl-oxygen fission).

β -Cholesterol was found to give a hydrogen sulphate (6c), isolated as the pyridinium and potassium salts, with sulphuric acid and acetic anhydride in carbon tetrachloride, indicating that the sulphate ester could be an intermediate in the acetylation of 3 β -cholesterol.

Reaction of β -cholesterol with sulphuric acid-acetic anhydride for 16 hrs at 20° gave 3 β -acetoxysterol (6b), characterised by its melting point. Thin layer chromatography of the sample showed the presence of only one compound while 3 α -acetoxysterol (7b) was shown to separate from the 3 β -acetate under the same conditions. Alkyl-oxygen fission to form a carbonium ion would be expected to lead to formation of a significant quantity of 3 α -acetate (7b) to give an epimer ratio of about 1:1. In addition carbonium ion formation might lead to elimination giving Δ^2 -cholestene (8) or Δ^3 -cholestene (9). The solvolysis of 3 β -tosyloxysterol (6d) in acetic

acid is reported³³ to yield the olefins (8) and (9) as major products; acetolysis of other 3-toluene-p-sulphonyloxy-steroids (saturated at C₅) gave³⁴ inversion of configuration at C₃, accompanied by a considerable proportion of elimination. Alkyl-oxygen fission by S_N2 attack on the C₃ carbon atom is unknown for acid catalysis and would lead to inversion to the 3α-acetate. Since the amounts of 3α-acetoxy-cholestane and cholestenes produced were negligible, alkyl-oxygen fission cannot have occurred and the reaction mechanism must involve attack on the oxygen atom of the hydroxyl group and acyl-oxygen fission.



The formation of cholestanol hydrogen sulphate appears to be rapid and complete. Sulphuric acid was present at the same concentration as β-cholestanol and therefore it can be taken that all of the cholestanol in the acetylation mixture was present as the sulphate ester. Since acetylation still proceeded it follows that the formation of the sulphate ester must also be reversible.

The above conclusion that the reaction involves acyl-oxygen fission was confirmed by the use of O¹⁸ enriched solvent in place of acetic anhydride-acetic acid of the natural enrichment. The product, cholestanyl acetate, was found to contain as many oxygen atoms incorporated from the solvent as benzyl acetate and half as many as p-anisyl acetate.

Since p-anisyl acetate cannot contain four oxygen atoms derived from the solvent (two oxygens is the maximum for one alcohol group), cholestanyl acetate must contain only one oxygen atom derived from the solvent. Therefore the alkyl-oxygen of the product must have remained attached to the steroid nucleus throughout the acetylation; alkyl-oxygen fission cannot have occurred.

Reaction of Cyclohexanol with Sulphuric Acid-Acetic Anhydride

The reaction of a fixed concentration of cyclohexanol (0.1M) with a fixed concentration of acetic anhydride (0.53M) at variable concentrations of sulphuric acid (10^{-4} - 10^{-2} M) showed a first order rate dependence on sulphuric acid (Graph 5). At fixed sulphuric acid (2×10^{-4} M) and acetic anhydride (2.12M) concentrations a first order dependence on alcohol concentration between 0.05 and 0.2M was found, with a transition to a zeroth-order dependence at higher concentrations (Graph 4). A first order dependence on the acetic anhydride/acetic acid ratio was observed at 0.1M alcohol and 10^{-3} M sulphuric acid (Graph 6).

The kinetic results described above are consistent with acetylation by attack of the hydroxyl oxygen atom on acetonium ion, Ac^+ , or a source of potential acetonium ion such as acetyl hydrogen sulphate or diacetyl sulphate. Acetylation by acetolysis of an intermediate alkyl sulphate would show a zeroth-order dependence on the alcohol concentration when the

sulphuric acid was present in excess if the formation of the cyclohexyl sulphate ester was complete and rapid. This zeroth-order dependence was found for steroids in the Westphalen rearrangement (see General Introduction), indicating that formation of the sulphate ester was complete for the tertiary steroids. It would be expected, therefore, that the equilibrium constant for formation of the cyclohexyl hydrogen sulphate would be even more favourable because of the smaller steric hindrance to formation in this case. Although the acetylation of cyclohexanol does show a zeroth-order dependence on alcohol at concentrations above about 0.2M, the reaction is first order in alcohol below this concentration which is still 1000 times the sulphuric acid concentration. Therefore rate-determining reaction of cyclohexyl hydrogen sulphate or of any species derived from it by a fast equilibrium must be rejected; this includes acetolysis of the sulphate ester by both direct displacement (S_N2) or by carbonium ion formation.

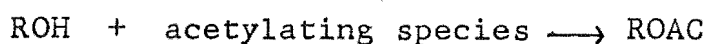
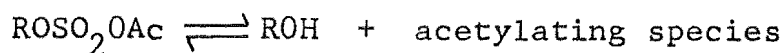
Although rate-determining reaction of an intermediate cyclohexyl sulphate has been ruled out, the first order dependence on alcohol does not exclude rate-determining formation of a cyclohexyl ester of acetyl hydrogen sulphate (sulphation). However a similar step has been shown¹⁴ to be a fast step in the carbonium ion forming reaction of a tertiary steroidal alcohol $3\beta,6\beta$ -diacetoxycholestan- 5α -ol (see General Introduction). Sulphation of cyclohexanol should be at least as fast as that of the tertiary steroid (1a) which

is more hindered and therefore faster than the carbonium ion formation for the latter alcohol. If the acetylation of cyclohexanol is slower than the carbonium ion formation for the steroid, then the formation of a sulphate ester for cyclohexanol must be a fast step in the acetylation.

It was not possible to measure the rates of reaction of cyclohexanol and the steroid (1a) under the same conditions, but the rates can be calculated on the basis of the observed rate dependences. The rates of reaction of both cyclohexanol and the steroid were measured at 2.12M acetic anhydride and 2×10^{-4} M sulphuric acid and different alcohol concentrations. The rate for the steroid (0.01M) was 2.2×10^{-7} moles l^{-1} sec^{-1} and for cyclohexanol (0.1M) was 2.9×10^{-5} moles l^{-1} sec^{-1} (Tables I and XI); the rate for 0.01M cyclohexanol is calculated to be 2.9×10^{-6} moles l^{-1} sec^{-1} . Therefore cyclohexanol would react 13 times faster than the steroid (1a) under these conditions. However the 6 β -methoxy (1b) and 6-deoxy (1c) steroids react 32 and 150 times faster than the 6 β -acetoxy compound respectively and both these compounds also show the zeroth-order dependence on alcohol characteristic of the rapid, equilibrium formation of the sulphate ester. Since these compounds would react faster than cyclohexanol, sulphate formation for the latter alcohol must be a fast step at this concentration. Both sulphation and acetylation will be first order in alcohol so sulphation should be a fast step at the alcohol concentrations actually used (0.05 - 1.0M).

The kinetic results therefore indicate that acetylation

of secondary alcohols with acetic anhydride-sulphuric acid involves acyl-oxygen fission and not alkyl-oxygen fission - a conclusion also reached on the basis of the absence of any inversion or elimination products in the acetylation of 3 β -cholestanol. Since the rate is dependent on alcohol, acetic anhydride and sulphuric acid, the transition state for the reaction must be obtained from these three reagents, probably by attack on the alcohol by an acetylating species derived from acetic anhydride and sulphuric acid. Under the reaction conditions used (excess alcohol) all the sulphuric acid is present as cyclohexyl hydrogen sulphate (ROSO_2OH) and therefore the acetylating species must be cyclohexyl acetyl sulphate (ROSO_2OAc). If acetyl hydrogen sulphate or diacetyl sulphate, formed from cyclohexyl acetyl sulphate, were the acetylating species the rate would show a zeroth-order dependence on cyclohexanol since this would be produced during the formation of the acetylating species. This can be demonstrated by the following outline.



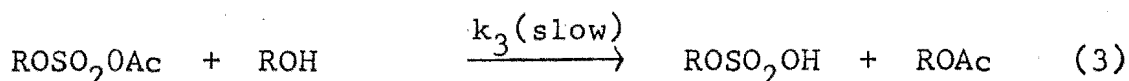
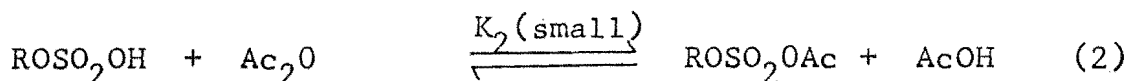
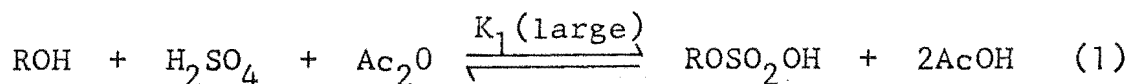
$$\text{rate} \propto [\text{ROH}] [\text{acetylating species}]$$

$$\text{i.e. rate} \propto [\text{ROH}] [\text{ROSO}_2\text{OAc}] / [\text{ROH}]$$

$$\text{i.e. rate} \propto [\text{ROSO}_2\text{OAc}]$$

This is independent of $[\text{ROH}]$ if the alcohol is present in excess.

The proposed mechanism is as follows.



The rate expression (k_3 rate-determining) is:

$$\begin{aligned} \text{rate} &= k_3 [\text{ROH}] [\text{ROSO}_2\text{OAc}] \\ &= k_3 K_2 [\text{ROH}] [\text{ROSO}_2\text{OH}] [\text{Ac}_2\text{O}] / [\text{AcOH}] \end{aligned}$$

This rate expression agrees with the observation of a first order rate dependence on alcohol and sulphuric acid added, since the latter is equal to the concentration of ROSO_2OH . A linear dependence of the rate on the ratio $[\text{Ac}_2\text{O}] / [\text{AcOH}]$ was observed (Graph 6) in agreement with the prediction from the above rate expression.

The zeroth-order rate dependence observed at alcohol concentrations above about 0.2M is explained if reaction (3) which is first order in alcohol becomes faster than reaction (2) which is independent of alcohol concentration. Then the rate-determining step is reaction (2) and the rate expression is as follows.

$$\begin{aligned} \text{rate} &= k_2 [\text{ROSO}_2\text{OH}] [\text{Ac}_2\text{O}] \\ &= k_2 [\text{H}_2\text{SO}_4] [\text{Ac}_2\text{O}] \end{aligned}$$

The reaction of cyclohexanol with acetic anhydride and sulphuric acid follows the same initial path as that of the tertiary 5 α -hydroxysteroids (1) in the same system; complete formation of the alkyl hydrogen sulphate occurs, followed by equilibrium conversion of a fraction of this into the alkyl acetyl sulphate. The tert-alkyl acetyl sulphate ionizes to the carbonium ion, but since a secondary carbonium ion would be much less stable, the sec-alkyl acetyl sulphate does not ionize but reacts with a molecule of alcohol, acetylating it.

Acetylation of Benzyl Alcohols

Benzyl and p-nitrobenzyl alcohols

The acetylation of benzyl alcohol showed a first order rate dependence on sulphuric acid, alcohol and the ratio of acetic anhydride to acetic acid (Graphs 7, 8 and 9), suggesting that the mechanism is similar to that proposed for cyclohexanol (p.77). The rate dependence on alcohol concentration did not change to zeroth-order at high alcohol concentrations as it did for cyclohexanol. Instead only a slight curvature of the rate plot was found; this could be due to slight solvent effects at the high benzyl alcohol concentrations (about 5%). It is unlikely that the rate of step (3) has not exceeded that of step (2) even at 0.5M alcohol. Although the rate of the overall reaction and hence step (3) was greater for benzyl alcohol than for cyclohexanol (3.8:1), the rate of step (2) would also be affected by the change in alcohol. This latter effect would however be

expected to be less than that for step (3) because of the greater separation of the R group from the reaction site for this step. The rate of acetylation of *p*-nitrobenzyl alcohol did exhibit a change in dependence on alcohol from first to zeroth-order at an alcohol concentration of about 0.2M and a rate of about 2×10^{-4} moles l^{-1} sec^{-1} . The rate at which this occurred for cyclohexanol was about 9×10^{-5} moles l^{-1} sec^{-1} ; this difference can probably be explained by a change in the rate of step (2). However benzyl alcohol did not show a clear change to zeroth-order at rates above 3×10^{-4} moles l^{-1} sec^{-1} and it is difficult to see why this does not occur.

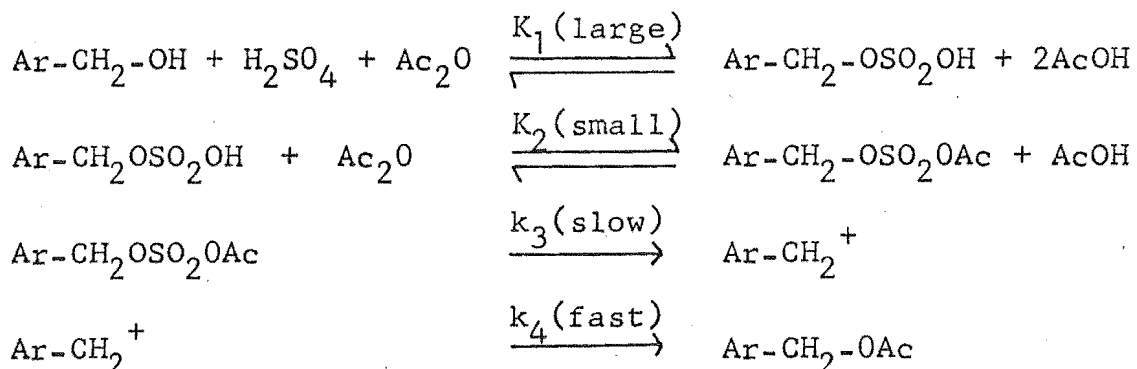
Further evidence that acetylation of benzyl alcohol involves acyl-oxygen fission came from the use of acetic anhydride-acetic acid enriched in O^{18} . The benzyl acetate formed was found to contain 1.05 oxygen atoms derived from the solvent (if it is assumed that cholestanyl acetate contains one oxygen from the solvent). This is almost half the number of oxygens incorporated into *p*-anisyl acetate. Therefore the acetylation of benzyl alcohol involves attack by the alcohol on an acetylating species, not the breaking of the C-O bond in the alcohol.

p-Anisyl alcohol

The reaction of p-anisyl alcohol with acetic anhydride and sulphuric acid was found to show a zeroth-order rate dependence on alcohol concentration (Table III). The variation between the rates was relatively large, about 14%, but the order dependence is clear. This zeroth-order dependence could be caused by the existence of a mechanism different from that for benzyl alcohol, carbonium ion formation, or by step (3) of the mechanism suggested for benzyl alcohol and cyclohexanol becoming faster than step (2) (cf. cyclohexanol above 0.2M).

The rate was much greater than that for benzyl alcohol under the same conditions (2% Ac_2O , $2 \times 10^{-4}\text{M}$ H_2SO_4) taken from Graph 8, the ratio being 8.6:1. This rate difference is much greater than that observed for the other substituted benzyl alcohols used (Table IX); for instance the rate for p-nitrobenzyl alcohol was 1.08 times that for benzyl alcohol. In addition electron-withdrawing substituents were found to cause a slight increase in rate which indicates that p-anisyl alcohol might be expected to react a little more slowly than benzyl alcohol.

Therefore p-anisyl alcohol must react with acetic anhydride-sulphuric acid by a mechanism different from that suggested for benzyl alcohol and p-nitrobenzyl alcohol. The mechanism suggested involves formation of a carbonium ion by alkyl-oxygen fission in the rate-determining step followed by reaction with acetic acid to give p-anisyl acetate.



The first two steps are the same as those for benzyl alcohol and the mechanism as a whole is similar to that proposed for 5 α -hydroxysteroids (General Introduction).

It is reasonable that carbonium ion formation is insignificant for benzyl alcohol while predominating for *p*-anisyl alcohol. Rate determining formation of a carbonium ion would be expected to be much more sensitive to substituent effects than attack on the oxygen atom of a benzyl alcohol, and through-conjugation of electron-donating substituents is possible in the former case.

The mechanism suggested for *p*-anisyl alcohol should lead to incorporation into the product acetate of two oxygen atoms from the solvent (twice as many as for benzyl alcohol). It was found by the use of O^{18} that the product contained 1.93 oxygens derived from the solvent. This indicates that the mechanism given above involving alkyl-oxygen fission is correct.

p-Methylbenzyl alcohol

The rate of reaction of p-methylbenzyl alcohol with acetic anhydride-sulphuric acid is plotted against alcohol concentration in Graph 11. The rate consists of two components, a zeroth-order component of 1.57×10^{-5} moles l^{-1} sec^{-1} and a first order component with $k_1 = 5.07 \times 10^{-4}$ sec^{-1} . This indicates that the reaction is between the two extremes observed for benzyl alcohol and p-anisyl alcohol; the mechanisms of carbonium ion formation and direct acetylation both contribute significantly to the overall rate. The rate of the direct acetylation component was compared with the rates for other substituted alcohols while that of the carbonium ion forming reaction was compared with the rate of acetylation of p-anisyl alcohol. The rate of the zeroth-order component for p-methylbenzyl alcohol (0.1M) is 0.27 times the overall rate for benzyl alcohol at the same concentration while the ratio for p-anisyl alcohol is 8.6:1. Therefore the acetylation of p-anisyl alcohol is 32 times faster than the zeroth-order component of that of p-methylbenzyl alcohol. This rate difference can be used with the Hammett σ^+ values for the two substituents to give an approximate value of ρ . The values of σ^+ are 0.78 for the p-methoxy substituent and -0.31 for p-methyl giving a difference of 0.47. The values of σ^+ are used for this calculation because the electron-donating para-substituent is able to through-conjugate with the positively charged reaction centre.

$\text{Log } (k_{\text{MeO}}/k_{\text{Me}})$ is 1.505 and $\sigma_{\text{MeO}}^+ - \sigma_{\text{Me}}^+$ is -0.47 giving an approximate value for ρ of -3.2. This can be compared with the values³⁶ for the solvolysis of benzyl tosylates in 96% acetone-water at 25°; for the more reactive substituents (*p*-MeO to H) ρ was -3.6 and for the less reactive substituents (*m*-MeO to *p*-NO₂) ρ was -1.4. This reaction was shown³⁷ to proceed by formation of the benzyl cation.

m-Chlorobenzyl alcohol

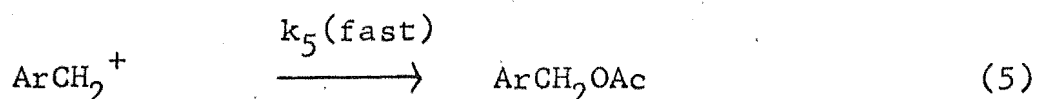
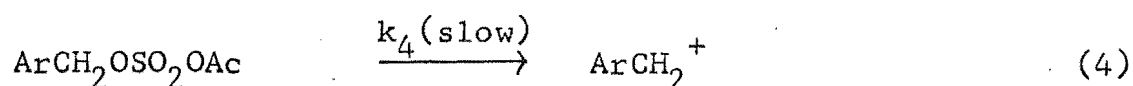
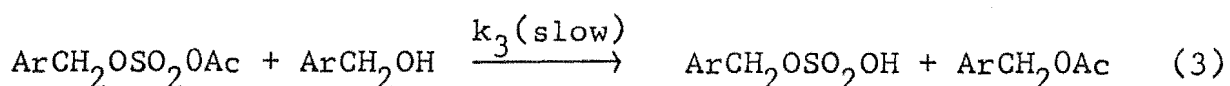
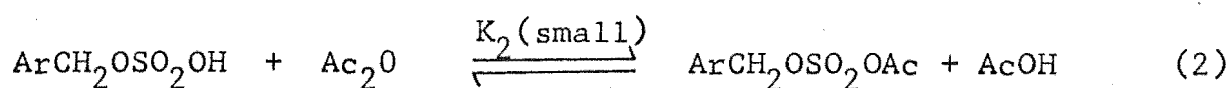
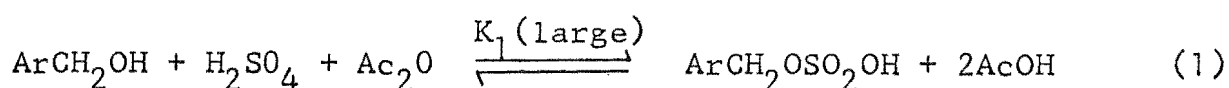
In the acetylation of *m*-chlorobenzyl alcohol a change of rate dependence from first to zeroth-order was observed at a rate of about 6.5×10^{-5} moles l⁻¹ sec⁻¹ (Graph 12). This rate is much lower than that at which the change occurred for *p*-nitrobenzyl alcohol (2×10^{-4} moles l⁻¹ sec⁻¹) and cyclohexanol (9×10^{-5} moles l⁻¹ sec⁻¹). The other substituted benzyl alcohols did not show a change in order up to a rate of 2×10^{-4} moles l⁻¹ sec⁻¹. It is difficult to see any explanation for the unusual behaviour of *m*-chlorobenzyl alcohol.

Substituent effects

The relative rates of acetylation of the substituted benzyl alcohols studied are summarised in Table IX. Apart from the *p*-methoxy substituent, the substituents exert little effect on the rate. Electron-withdrawing substituents appear to exert a slight accelerating effect on the rate but this is very small, ρ being about +0.2. This value is so small that

it can effectively be considered to be zero and indicates that the reaction site is quite far removed from the ring. For a reaction involving charge on the benzylic carbon the ρ value for electron-withdrawing substituents was found³⁶ to be -1.4. However acid hydrolysis of benzyl esters has been shown³⁸ to be very insensitive to the effects of substituents in the aromatic nucleus; the ρ value was said to be nearly zero.

The very low ρ value for the acetylation of most benzyl alcohols indicates that the mechanism involves attack by the hydroxyl oxygen on the acetylating species, not the formation of a benzyl cation which would not be expected for a primary alcohol. In the following mechanism step (3) dominates for all substituents except *p*-methyl and *p*-methoxy; steps (4) and (5) contribute to the rate for *p*-methyl and dominate the reaction for *p*-methoxy.

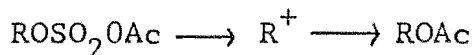


Reaction of 1-Methylcyclohexanol with $\text{Ac}_2\text{O}/\text{H}_2\text{SO}_4$

The reaction of 1-methylcyclohexanol with acetic anhydride-sulphuric acid showed a first order rate dependence on the ratio of acetic anhydride to acetic acid (Table X). The rate dependence on alcohol was more complex; the overall rate is made up of two components, one first order in alcohol with $k_1 = 5.45 \times 10^{-5} \text{ sec}^{-1}$ and the other zeroth-order in alcohol with a rate of $5.2 \times 10^{-6} \text{ moles l}^{-1} \text{ sec}^{-1}$. The first order reaction is probably direct acetylation on the oxygen atom of the alcohol (as found for cyclohexanol) while the zeroth-order component probably involves carbonium ion formation. This carbonium ion can either be captured by acetic acid (leading to acetylation) or eliminate to yield one or both of the two possible olefins, 1-methylcyclohexene and methylenecyclohexane. The yield of acetate was found to be only about 70% indicating the formation of some olefin by the carbonium ion mechanism (almost 100% acetate formation had been found for cyclohexanol).

A carbonium ion forming reaction would be expected to be more significant for the tertiary alcohol, methylcyclohexanol than for cyclohexanol. The first order reaction would be expected to be a little slower than for cyclohexanol because of the additional steric hindrance from the methyl group. This hindrance should not be large and the reduction in the rate of direct acetylation by a factor of about 5 from cyclohexanol to methylcyclohexanol would seem reasonable. Therefore the existence of the following two competing reactions of the

sulphate ester can be satisfactorily explained.

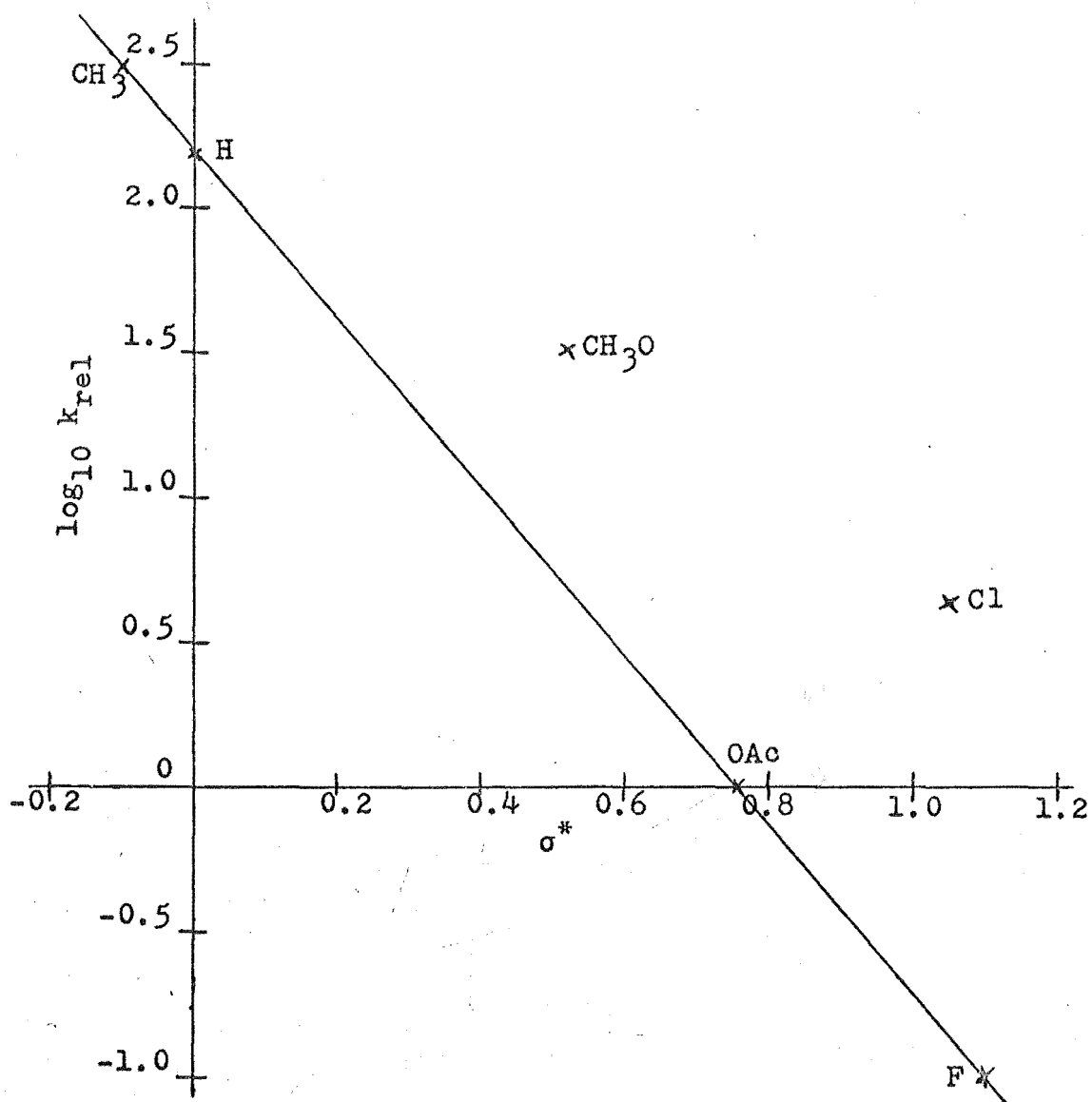


Reactions of 6 β -Substituted-3 β -acetoxystrophan-5 α -ols

The relative rates (k_{rel}) for the reactions of 6 β -substituted-3 β -acetoxystrophan-5 α -ols (1) with sulphuric acid and acetic anhydride are given in Table XI. The values of $\log k_{\text{rel}}$ are plotted against σ^* in Graph 15; σ^* values for the X-CH- groups are assumed to be the same as those listed by Taft¹⁸ for the X-CH₂- groups. There appears to be some uncertainty regarding the value of σ^* for the acetoxy substituent. The value given by Taft and Kreevoy³⁹ for AcOCH₂ (+0.76) was calculated from the values of σ^* for HO-CH₂ and CH₃-CO-CH₂ and was found to fit moderately well their Hammett plot for the hydrolysis of ketals. However a value of +0.85 would have fitted this plot equally well. A different value of σ^* can be obtained from the relationship⁴⁰ $\sigma_{\text{I}} = 0.45\sigma^*$; σ_{I} for the acetoxy group is given⁴⁰ as +0.39 and from this σ^* is calculated to be +0.87. No indication is given whether this value of σ_{I} is calculated from other substituents or determined from a reaction so the σ^* value of +0.87 may be no more reliable than that of +0.76. The former value was found by Thawley¹⁶ to fit the line for the other substituents reasonable well for the 3 β -substituted-6 β -acetoxy compounds.

GRAPH 15

σ^* for 6 β -substituents against log relative rate
for C₅ carbonium ion formation



However Lewis¹⁵ found a better fit using the latter value in his study of 3 β -fluoro-6 β -substituted compounds. It seems therefore that the use of either value is justifiable and the value of +0.76 was used in this work because it gave a better fit with the 6 β -Me, 6-H and 6 β -F substituents.

The values of k_{rel} for the 6 β -methoxy (1b), 6-deoxy (1c), and 6 β -methyl (1d) compounds differ from those previously published^{14,16b}; the previous value for 6 β -methoxy¹⁴ was found to be incorrect and the values of k_{rel} for the 6 β -Me and 6-H substituents originally published^{16b} were calculated using this incorrect value as a basis for comparison. In the present work k_{rel} for each of these three substituents has been determined by direct comparison with the 6 β -acetoxy compound (1a) under the same conditions. The value of k_{rel} for the 6 β -chloro compound previously published¹⁴ has been confirmed.

In Graph 15 a good straight line can be drawn through the points for the 6 β -Me, 6-H and 6 β -F substituents and the point for 6 β -OAc using a σ^* value of +0.76. The slope of this line, ρ^* , is -2.8. This value is between those published for 3 β -substituted-6 β -acetoxy compounds¹⁶ (-3.4) and 6 β -substituted-3 β -fluoro compounds¹⁵ (-2.3).

There is no evidence that the reaction of the 6 β -methyl and 6-deoxy compounds with sulphuric acid-acetic anhydride to give non-rearranged olefins does proceed by the heterolysis of the 5 α -acetylsulphate as opposed to the rate-determining loss of water from the protonated 5 α -hydroxy group. However

it is reasonable to suppose that the same mechanism applies for all 6 β -substituents. Even if this is not so, the rates presented do represent the upper limit for the rate of formation of the C₅ carbonium ion from a 5 α -acetylsulphate and lead to a maximum value for ρ^* of -2.8.

The points for the two substituents 6 β -MeO and 6 β -Cl lie above the line for the other four substituents. This may be due to anchimeric assistance by the neighbouring group; this participation has been suggested¹⁴ to cause the increased yield of 5 α -acetate in the reactions of the 6 β -methoxy, 6 β -bromo and 6 β -iodo compounds. However, although the methoxy substituent is notably^{41a} capable of neighbouring group participation, the chloro substituent is considered^{41b} to be much less effective and little evidence for the participation of this substituent was found¹⁴ from the product analysis. In addition the 6 β -acetoxy substituent might be expected to participate by stabilising the carbonium ion formed as has been suggested for trans-2-acetoxycyclohexyl p-toluenesulphonate^{41c}. However the yield of 5 α -acetate from the 6 β -acetoxy compound is low¹⁴ and the rate does not appear to be increased much by participation by the acetoxy substituent although some increase is possible if the σ^* value of +0.86 is correct. Neighbouring group participation in this system must therefore remain in doubt at present.

*Rate" wrong, didn't measure main chol, methyl group
just diff. & effect on CD* 90

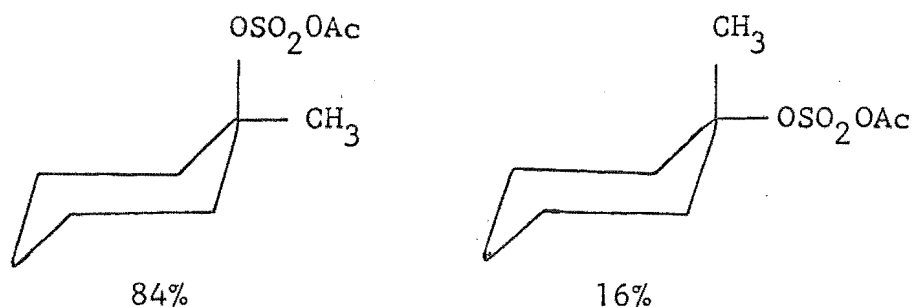
Comparison of Rates for Methylcyclohexanol & 5 α -Hydroxysteroids

The rates of reaction of methylcyclohexanol and the 6-deoxy compound, 3 β -acetoxysteroid-5 α -ol (1c), with acetic anhydride-sulphuric acid were measured at identical concentrations of sulphuric acid ($2 \times 10^{-4}M$) and acetic anhydride (2.12M). Although the concentrations of alcohol used differed, the reaction is zeroth-order in steroidal alcohol¹⁴ at the concentrations used and only the zeroth-order component of the rate for methylcyclohexanol is considered in the comparison; therefore the two rates can be compared directly. The mean rate for the steroid was 3.3×10^{-5} moles l^{-1} sec^{-1} . The rate of the zeroth-order (carbonium ion) component of the reaction of methylcyclohexanol was 5.2×10^{-6} moles l^{-1} sec^{-1} . The ratio of the rates is 6.6.

A comparison of the rates for methylcyclohexanol and the unsubstituted 5 α -hydroxysteroid, cholesterol (10) would obviously be of interest. The two hydroxy groups should be in similar electronic environments and the difference in rates should be caused by steric effects. Unfortunately cholesterol-5 α -ol would react too rapidly to allow its rate to be measured by the method used for the other steroids. However the rate for this compound can be approximately estimated from the observed rate for 3 β -acetoxysteroid-5 α -ol (1c). Thawley has shown¹⁶ that the introduction of a 3 β -acetoxy substituent into 6 β -acetoxysteroid-5 α -ol reduced the rate by a factor of 13.2. Since 3 β -acetoxysteroid-5 α -ol reacts 6.6 times faster

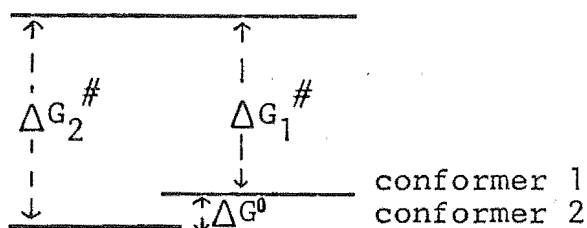
than methylcyclohexanol and a 3 β -acetoxy substituent reduces the rate by a factor of 13.2 it would be expected that cholestan-5 α -ol would react about 87 times faster than methylcyclohexanol.

This increased rate is probably due to steric assistance to the reaction, not to any conformational difference between the two alcohols. Cholestan-5 α -ol and its acetyl-sulphate ester both have the 5-substituent fixed in the axial conformation while methylcyclohexanol and its ester are found as an equilibrium mixture of two conformers. There is little difference between the positions of the conformational equilibria for the latter two compounds since the free energy differences between the axial and equatorial conformations are almost the same for hydroxyl and ester groups⁴². The free energy difference for the *p*-toluene-sulphonyl group is⁴² 0.7 kcal/mole and this value can be used for the acetyl sulphate ester because of the small effect of ester groups. The conformational free energy difference for a methyl substituent is⁴² 1.7 kcal/mole. Since in 1-methylcyclohexyl acetyl sulphate the methyl group is axial when the ester is equatorial and vice versa, the free energy difference between the two conformers of this ester can be estimated to be about 1.0 kcal/mole. The conformer with the methyl group equatorial and the ester group axial will be the most favoured and about 84% of the compound will be in this form.



Therefore the ester group is mainly axial in the acetyl sulphates of both cholestan-5 α -ol and methylcyclohexanol and conformational effects are not responsible for the difference in rates between these two compounds.

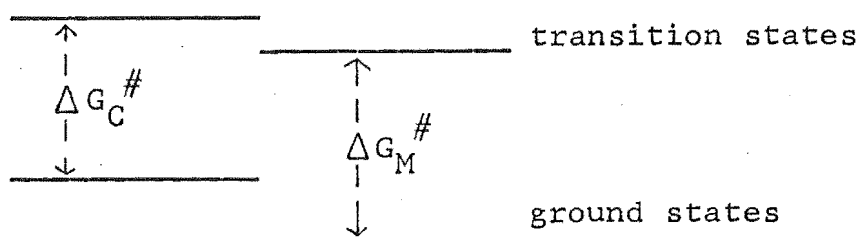
Although the conformer with the methyl group axial is more stable, it will react more slowly than the other conformer. The transition states for the reactions of both conformers of the acetyl sulphate should be very similar, being very close to carbonium ions, and can probably be considered to be of the same energy. Therefore the relative rates for the two conformers will be determined by the difference in free energies between the conformers of the ester.



The ratio k_1/k_2 will be equal to $\exp(-\Delta G_1^\ddagger/RT)/\exp(-\Delta G_2^\ddagger/RT)$ i.e. $\exp(\Delta G^\circ/RT)$. From the value for ΔG° of 1.0 kcal/mole, k_1/k_2 is 5.4. Therefore the conformer with the methyl group axial will react 5.4 times faster than the conformer with the

methyl group equatorial. This rate difference is of the same order as that found⁴³ for the acetolysis of cis and trans 4-t-butylcyclohexyl tosylates (3.2) which involves a carbonium ion mechanism. Because the ratio of the concentrations of the two conformers is the inverse of the ratio of their rate constants, their contributions to the overall rate will be equal. From the relationship⁴⁴ $k(1+K) = k_e + Kk_a$, the overall rate constant, k , for the ionization of methylcyclohexyl acetylsulphate is 1.7 times that of the more stable conformer (ester group axial).

The difference between the rate of reaction of cholestan-5 α -ol and the total rate for both conformers of methylcyclohexanol is therefore probably due to steric assistance. The steric strain in the alcohol and its sulphate ester will be greatly relieved when the leaving group departs from the tetrahedral ester forming a trigonal carbonium ion. The relief of strain will be greater for a more hindered alcohol since there will be less difference in energies between the transition states for two alcohols than between the alcohols themselves and the ester intermediates. Therefore it is to be expected that the more hindered alcohol would react more rapidly in a carbonium ion forming reaction. The possibility of such steric assistance has been suggested for the solvolysis of tertiary alkyl halides⁴⁵.



cholestan-5 α -ol methylcyclohexanol

$$k_C = A_C \exp(-\Delta G_C^\# / RT) \quad k_M = A_M \exp(-\Delta G_M^\# / RT)$$

If it is assumed that there is little difference between the frequency factors, A , for the two reactions, then

$$\ln k_C / k_M = (\Delta G_M^\# - \Delta G_C^\#) / RT$$

Therefore if $\Delta G_M^\#$ is greater than $\Delta G_C^\#$, k_C is greater than k_M .

The ratio of k_C for cholestanol to the overall k for methylcyclohexanol is 87:1 and $k_{\text{overall}} / k_{\text{axial}}$ is 1.7.

Therefore the ratio of the rate constants for the ionization of the two axial acetyl-sulphates is 148:1. This means that the difference in the free energies of activation of cholestan-5 α -ol acetylsulphate and the more stable (axial ester group) conformer of methylcyclohexyl acetyl sulphate is about 3.0 kcal/mole.

Conclusion

The acetylation of primary and secondary alcohols by acetic anhydride-sulphuric acid usually involves attack by the alcohol on the acyl function of the acetylating agent (acyl-oxygen fission). However for *p*-anisyl alcohol a

carbonium ion intermediate, formed by alkyl-oxygen fission, is involved while for *p*-methylbenzyl alcohol both types of reaction occur. The reaction of tertiary alcohols with acetic anhydride-sulphuric acid also proceeds through a carbonium ion intermediate although there is some contribution from acyl-oxygen fission for 1-methylcyclohexanol. Steric assistance to the reaction of tertiary alcohols is likely.

PART II

THE REACTION OF $3\beta,6\beta$ -DIACETOXYCHOLESTAN- 5α -OL
WITH FLUOSULPHONIC ACID

INTRODUCTION

The reaction of sulphuric acid and acetic anhydride with 3 β ,6 β -diacetoxystrostan-5 α -ol (1a) to give the rearranged compound 3 β ,6 β -diacetoxy-5 β -methyl-19-norcholest-9-ene (3a) (discussed in General Introduction) has been shown¹⁴ to proceed through the formation of a sulphate ester at the 5 position followed by acetylation to an acetylsulphate ester (ROSO₂OAC) which gives rise to a C₅ carbonium ion. It was considered that fluosulphonic acid should behave similarly by forming a fluosulphate ester (ROSO₂F) which could give rise to a C₅ carbonium ion in the same way. Therefore it might be expected that reaction of the 5 α -hydroxy steroid (1a) with fluosulphonic acid at -78° would yield the $\Delta^{9(10)}$ -diacetate (3a).

However the "Backbone rearrangement" of a C₅ carbonium ion has been shown⁴⁶ to proceed further for the reaction of 3 β ,5 α ,6 β -triacetoxystrostan (2a) with boron trifluoride in acetic anhydride to give the 5,14-dimethyl-18-19-bisnor-enantio-cholest-13(17)-ene derivative (11). There have been only two cases reported where an olefinic product has been found with the rearrangement concluded at an intermediate position of the cholestane nucleus. The reaction of 3 β -acetoxy-5 α ,6 α -epoxy-4,4-dimethylcholestane (12) with boron trifluoride in benzene has been found⁴⁷ to give, among other products, 18% of a compound having the 8(14)-olefinic structure

(13). Under similar conditions 3 α -acetoxy-5 α ,6 α -epoxycholestane (14) gave⁴⁸ 3 α -acetoxy-5 β -methyl-6 α -hydroxy-19-norcholest-8(14)-ene (15) in 27% yield. In all other known cases of migration of the 19-methyl group to the 5 β -position the product has been either the $\Delta^{9(10)}$ or the $\Delta^{13(17)}$ compound.

Deno and his associates have shown⁴⁹ that carbonium ions can be observed by NMR at -50° in fluosulphonic acid; it was therefore intended in the present work to observe the carbonium ion formed from 3 β ,6 β -diacetoxycholestan-5 α -ol (1a) and follow its rearrangement along the cholestane skeleton if this rearrangement proceeded at a reasonable rate. A large scale reaction was carried out at -78° for 48 hrs and an attempt made to identify the rearrangement products before the observation of the carbonium ion was tried. It was then found that the rearrangement was effectively complete within the time necessary to record the NMR spectrum and could therefore not be followed.

DISCUSSION

Reaction of 3 β ,6 β -Diacetoxycholestan-5 α -ol with FSO₃H

The reaction of 3 β ,6 β -diacetoxycholestan-5 α -ol (1a) with fluosulphonic acid for 48 hrs was shown by tlc to yield five compounds; these compounds were separated by column chromatography and preparative tlc. The first of these had an r_f value approaching unity for tlc in benzene and was thought to be a diene, a product of further reaction of an initial reaction product. Since the rearrangement was later shown to be complete in about 15 mins although the reaction mixture was allowed to stand for 48 hrs further reaction is quite likely to have occurred. The second and third compounds represented only a small fraction of the total reaction mixture, while the major products were the fourth and fifth compounds to come off the column. The fifth compound has been shown to have the structure (16) and will be referred to as this throughout this thesis; the fourth compound is thought to be (17a) and will be referred to as this although the structure has not been proved. All attempts to crystallise the products failed.

Structure of Compound 16

Compound 16 analysed correctly for C₃₁H₅₂O₅ and the mass spectrum confirmed that it was a hydroxy-diacetate of mass 504; the infrared spectrum showed the presence of an

alcohol and an acetate. Attempted acetylation with acetic anhydride-pyridine at 100° and oxidation with chromium trioxide-sulphuric acid both failed, indicating a tertiary alcohol.

Compound 16 was dehydrated with thionyl chloride in pyridine to give an oil showing an olefinic proton in the NMR at $\delta=5.55$ ppm; the UV extinction coefficient at $200\text{ m}\mu$ was high. These indicate that the oil probably consisted of a mixture of two olefinic compounds with double bonds at the 7-8 (18a) and 8-14 (19a) positions. The $\Delta^{7(8)}$ olefin would be expected to show an NMR peak at 5.55 ppm and the $\Delta^{8(14)}$ compound should have a high extinction coefficient⁵⁰.

Hydrolysis of this olefinic oil gave an olefin-diol. Ozonolysis of this diol gave a compound with all the ketone groups present in either six-membered rings or a straight chain environment; there was no evidence for the presence of a significant amount of aldehyde. This product is thought to be mainly of the structure (20) indicating that the olefin-diol had its double bond in the 8-9 position (17b). This is contrary to the UV and NMR data for the olefin-diacetates (18a) and (19a) but is possible that the double bond migrated during ozonolysis.

Oxidation of the olefin-diol with chromic acid-acetone gave a diketone. The IR and UV spectra suggested the presence of a conjugated ketone and the position of maximum UV absorption ($245\text{ m}\mu$) showed good correlation with the position predicted from Woodward's rules for the 6-keto- $\Delta^{7(8)}$ -

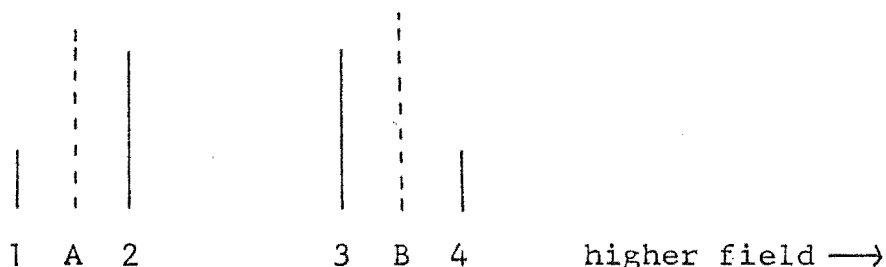
structure (21) (244 $m\mu$). The extinction coefficient of 4700 was lower than expected (ca 10,000) and suggested the presence of some compound with the double bond at a different position, perhaps 8-14 (22). Hydrolysis of the reaction product (16) followed by oxidation with chromic acid to the diketone (23) and dehydration with thionyl chloride gave an oil which gave similar UV and IR spectra to the mixture (21) and (22) above.

Because of the strong possibility of isomerization of the olefinic double bond in the above compounds it is not possible to gain positive evidence for the position of the double bond. However there is a considerable likelihood that the reaction product has its alcohol group at the 8 position (16) since all the possible olefins suggested involve a double bond with one end at the 8 position.

Further proof of the structure came from the NMR spectrum of the hydroxy-diketone (23), see Table XII. The C_7 methylene protons occurred as an AB quartet, the lower field peaks at $\delta 2.95$ and $\delta 2.73$ ppm, $J_{AB} = 15$ cps. These peaks were further downfield than those normally found for protons α to a ketone; cyclohexanone has a peak at 2.25 ppm and the rearranged 3.6-diketo- $\Delta^{13(17)}$ -compound (24) has peaks⁵¹ in the region 2.16 to 2.55 ppm. The pair of peaks at 2.95 and 2.73 ppm collapsed to a singlet at 2.83 ppm on irradiation with a difference frequency of + 40 cps. Because of the large number of protons absorbing in the region centred at $\delta 2.16$ ppm (the region where the other two peaks of the quartet would occur)

it was not possible to distinguish clearly the higher field peaks of the quartet.

In such an AB system the peaks are labelled as shown; the following treatment is based on that of Jackman⁵².



J_{AB} is taken as the frequency difference between 1 and 2, i.e. 15 cps, $\delta_A - \delta_B$ is taken as the difference frequency which collapses the doublet, 40 cps. Then:

$$\begin{aligned} \delta_1 - \delta_3 = \delta_2 = \delta_4 &= \left[(\delta_A - \delta_B)^2 + J_{AB}^2 \right]^{\frac{1}{2}} \\ &= 42.7 \end{aligned}$$

Therefore peaks 3 and 4 should be found at frequencies 43 cps less than peaks 1 and 2 respectively. Peaks 1 and 2 are at 179 and 164 cps so that peaks 3 and 4 should be found at 136 and 121 cps. The position of the centre of gravity of each pair is found by taking the centre of gravity of the complete AB system, midway between peaks 2 and 3 or 1 and 4, and adding or subtracting $\frac{1}{2}(\delta_A - \delta_B)$. The centre of the AB system is at 150 cps so δ_A is 170 cps and δ_B is 130 cps. On irradiation with a difference frequency of 40 cps the doublet was found to collapse to a broad singlet centred at 170 cps as expected from this treatment. The relative intensities of the peaks,

I_1 , can also be theoretically determined.

$$\begin{aligned} I_1 = I_4 &= 1 - J_{AB} \left[(\delta_A - \delta_B)^2 + J_{AB}^2 \right]^{-\frac{1}{2}} \\ &= 0.65 \\ I_2 = I_3 &= 1 - J_{AB} \left[(\delta_A - \delta_B)^2 + J_{AB}^2 \right]^{-\frac{1}{2}} \\ &= 1.35 \end{aligned}$$

So the relative intensities of peaks 2 and 1 are expected to be 1.35 and 0.65, i.e. 2.08:1.

The compound 3-keto-6 β -methylcholestan-5 α -ol (25) has the C_4 methylene protons in a similar but not identical environment to the C_7 protons in compound (23) and shows similar behaviour to this compound. In compound (25) it was possible to see all four peaks of the geminal AB system at δ 3.05, 2.81, 2.07 and 1.84 ppm, $J_{AB} = 14.5$ cps. The lower field peaks collapsed to a singlet on irradiation with a difference frequency of + 58 cps and the higher field peaks with - 58 cps.

For this compound J_{AB} is 14.5 cps, $\delta_A - \delta_B$ is 58 cps.

Then:

$$\begin{aligned} \delta_1 - \delta_3 = \delta_2 - \delta_4 &= \left[(\delta_A - \delta_B)^2 + J_{AB}^2 \right]^{\frac{1}{2}} \\ &= 59.8 \text{ cps} \end{aligned}$$

Therefore peaks 3 and 4 are expected to be found at frequencies 60 cps less than peaks 1 (183 cps) and 2 (168.5 cps) respectively, that is at 123 and 108.5 cps. Peaks were actually found at 124.5 and 110.5 cps showing reasonable agreement with the predicted positions. The centre of the system is at 146 cps and so the two pairs of peaks should collapse to

singlets at 175 and 117 cps. On irradiation with a difference frequency of ± 58 cps the peaks were found to collapse to singlets at 176 cps and 117 cps; again these show good agreement with the predicted frequencies.

$$I_1 = I_4 = 1 - 14.5/59.8 \\ = 0.758$$

$$I_2 = I_3 = 1.242$$

Therefore the ratio of the intensities of the peaks should be 1.64:1; the ratio measured from the integral of the spectrum was about 1.8:1.

The spin-decoupling behaviour of the spectrum of the hydroxy-diketone and the similarity of the spectrum to that of 3-keto-6 β -methylcholestan-5 α -ol (25) are good evidence for the assignment of the structure of the hydroxy-diketone as the 8-hydroxy-6-keto-compound (23) and the structure of the reaction product as 3 β ,6 β -diacetox-5 β -methyl-8 α -hydroxy-19-norcholestane (16).

The 8-hydroxy group of compound (16) is taken to be α rather than β because the latter would involve greater steric strain. The 8 α -hydroxy compound would have the 8 α -hydroxy group and the 14 α -hydrogen cis to each other, requiring ring C to be in skew-boat form. However the 8 β -hydroxy compound would have a cis ring junction between rings B and C requiring both rings to be in the more energetic skew-boat form. Therefore the 8 α -hydroxy structure would be expected to be

more stable. In addition a cyclic mechanism involving the 5 α -acetylsulphate in the starting material would be possible and if such a mechanism were involved it would require attack from the α -face at the 8 position.

Structure of Compound 17a

Compound 17a was shown by its infrared spectrum to contain at least one acetate; the NMR spectrum confirmed the presence of two acetate groups and showed the absence of a trisubstituted olefinic double bond. The ultraviolet spectrum had an extinction coefficient of 3800 at 200 m μ and addition to tetranitromethane gave an orange colour. This is consistent with the presence of a tetrasubstituted double bond not exocyclic to any ring as in structure (17a) but not with the presence of a tetrasubstituted double bond exocyclic to two rings. For the latter system, (3) or (19a), the extinction coefficient would be expected to be higher⁵⁰, about 10,000.

The compound was hydrolysed to the diol (17b) and then subjected to ozonolysis. The infrared spectrum of the product indicated the presence of two ketones in six-membered or larger rings or straight chains, consistent with the structure (20). This suggested that the olefin-diacetate had the double bond in the 8-9 position (17a) and not the 8-14 position (19a) since the latter would give an ozonolysis product with one ketone in a five-membered ring (ring D).

The olefin-diol (17b) was oxidised with chromic acid in acetone to the diketone (26). The infrared spectrum of this compound included an absorption at 1738 cm^{-1} ; this is in the range for ketones in five-membered rings. However it is difficult to see how a five-membered ring ketone could be formed in this system unless isomerization of the double bond to the 8-14 position followed by breaking of the double bond by oxidation led to the formation of the 14-ketone. This appears unlikely.

The diol was also oxidised under milder conditions (chromium trioxide in pyridine) and then reacted with oxalic acid⁵³ and later sulphuric acid in chloroform⁵⁴ in an attempt to bring the double bond into conjugation at the 7-8 position (21). No evidence of conjugation was found in the infrared or ultraviolet spectra. These unsuccessful attempts to form the conjugated ketone (21) cast some doubt on the assignment of the structure of the reaction product as the $\Delta^{8(9)}$ -compound (17a) since isomerization should occur in this compound under conditions where it has been shown to occur for other ketones^{53,54}. However no other reasonable possibilities for the structure can be seen.

The possibility of converting the olefin-diacetate into the 8-hydroxy compound (16) remained; this would have provided good evidence for the assignment of the structure (17a) to the olefin-diacetate. Brown has shown⁵⁵ that olefins can be converted into alcohols by treatment with

mercuric acetate followed by sodium borohydride but the method had not been tried for steroids. Cholest-5-ene was treated by this method in both tetrahydrofuran and dimethyl-sulphoxide as solvents but only the starting material was recovered. This is probably due to the low solubility of the steroid in both solvents; the simpler olefins used by Brown had been soluble in tetrahydrofuran. Because the method was found to be unsatisfactory for the less hindered and therefore more reactive cholest-5-ene it was not tested on the olefin-diacetate (17a).

Epoxidation with monoperphthallic acid followed by hydrolysis and oxidation might have yielded the hydroxy compound (16) but the NMR spectrum of the product did not show the presence of the peaks at δ 2.95 and 2.73 ppm characteristic of this compound and the product appeared from the methyl region of the spectrum to have decomposed.

Although the only evidence for the assignment of the structure (17a) to this compound is the rather inconclusive spectral data, the assignment of the 8α -hydroxy structure (16) to the other major product of the reaction provides some justification for regarding both compounds as formed from a carbonium ion at C_8 . Since the spectral evidence rules out the $\Delta^{7(8)}$ and $\Delta^{8(14)}$ structures for the olefinic product, the $\Delta^{8(9)}$ structure (17a) must be regarded as reasonable.

TABLE XII
NMR data (in ppm)

Compound	methyl peaks	R-CH ₂ -CO	C ³ -H, C ⁶ -H, etc
3,6-diOAc-8-OH (16)	0.91, 0.87, 0.82	2.02, 1.97	5.03, 4.76
3,6-diOAc-7(8)-ene(18a)	0.91, 0.87, 0.82	1.98, 1.95	5.56($\frac{3}{4}$ H), 5.21(1H), 5.21 & 5.03(1H)
3,6-diketone-8-OH (23)	1.26, 0.92, 0.87, 0.82	2.95, 2.73 2.42, 2.30	-
3-keto-6Me-8-OH (25)	0.92, 0.82, 0.72 0.68	3.05, 2.81 2.07, 1.84	-
3,6-diOAc-8(9)-ene(17a)	0.98, 0.90, 0.87 0.82	1.98 (6H)	5.00, 4.50

EXPERIMENTAL

Melting points are uncorrected. Optical rotations were determined for chloroform solutions. Infrared absorption measurements were carried out in carbon disulphide solutions and recorded with a Perkin Elmer model 337 or 421 instrument. Ultraviolet absorption data were obtained in ethanol or cyclohexane solutions and recorded with a Beckmann DK-2A spectrophotometer. Nuclear Magnetic Resonance spectra were recorded for carbon tetrachloride or deuteriochloroform solutions in a Varian A-60 spectrometer with TMS and CHCl_3 as internal standards. Alumina used for chromatography was Peter Spence, Grade H, deactivated by the addition of 5% of 10% aqueous acetic acid. Silica gel used for chromatography was J. Crosfield and Sons. Thin layer chromatography was carried out on silica gel; benzene and chloroform-acetone mixtures were used for developing chromatograms and the visualising agents used were antimony trichloride in chloroform, phosphomolybdic acid in ethanol and iodine in chloroform. Light petroleum refers to the fraction of b.p. 50-70°. The mass spectrum was run by Dr A. Fischer at the University of Sussex.

Cholestane-3 β ,5 α ,6 β -triol

To a solution of 5 α ,6 α -epoxycholestan-3 β -ol (58g) in acetone (1000ml) and water (50ml) was added perchloric acid

(25 drops). The mixture was warmed to 90° and kept at that temperature for 20 mins. The reaction mixture crystallised to give impure cholestane- $3\beta,5\alpha,6\beta$ -triol (40g), m.p. $153-158^{\circ}$.

$3\beta,6\beta$ -Diacetoxycholestan- 5α -ol (1a)

A solution of cholestane- $3\beta,5\alpha,6\beta$ -triol (38g) in acetic anhydride (70ml) and pyridine (100ml) was allowed to stand overnight at 20° . The steroidal material was extracted into methylene chloride and the solution washed with dilute H_2SO_4 and sodium bicarbonate and dried with $MgSO_4$. After removal of the solvents the crude product was crystallised from acetone to give $3\beta,6\beta$ -diacetoxycholestan- 5α -ol (18g) as needles, m.p. $160-161^{\circ}$. (Lit²¹. m.p. 166°).

Reactions of (1a) with Fluosulphonic Acid

A solution of $3\beta,6\beta$ -diacetoxycholestan- 5α -ol (1a) (5g) in methylene chloride (60ml) was cooled in a dry ice-acetone bath. Fluosulphonic acid (10ml) was added slowly at -78° and the mixture kept at this temperature for 48 hrs with constant stirring. The mixture was poured into water, extracted with ether or methylene chloride, washed with aqueous $NaHCO_3$ and dried with $MgSO_4$. Removal of the solvent under vacuum gave an oil (4.5g), shown by tlc to contain five compounds. The reaction was carried out several times to obtain enough material to characterise the products which were separated by adsorption on alumina. The results quoted below are for one

representative reaction of 5 g starting material, separated on 300g alumina.

Elution with light petroleum gave an oil (74mg),
 λ_{\max} 248 m μ (ϵ 4800).

Elution with light petroleum-benzene (9:1-1:1) gave an oil (550mg), shown by tlc to contain two compounds.

Elution with light petroleum-benzene (1:3) and benzene gave a glass (1.2g), considered to be the olefin (17a),
 $[\alpha]_D -8^\circ$.

Elution with benzene-ether (18:1-4:1) gave a glass (2.3g), later shown to be the diacetate (16), $[\alpha]_D -61^\circ$, ν_{\max} 3510, 1750, 1740 and 1250 cm^{-1} . (Found: C, 74.1; H, 10.3.
 $\text{C}_{31}\text{H}_{53}\text{O}_5$ requires C, 73.7; H, 10.5%)

The fractions of each compound from four reactions were combined and re-chromatographed on silica gel to obtain purer compounds. For a later preparation chromatography by adsorption on silica gel followed by preparative tlc on silica gel was used instead of chromatography on alumina.

Attempted Oxidation and Acetylation of the Diacetate (16)

a) Oxidation. The diacetate (77mg) was dissolved in acetone (5ml) and a solution of 8N chromic acid (30g CrO_3 , 25.6ml H_2SO_4 in 80ml water) added dropwise until a permanent orange colour persisted. The reaction mixture was allowed to stand for 5 mins. Sodium metabisulphite was added to neutralize the excess chromic acid and the mixture poured into

water. The steroidal material isolated via ether was shown to be identical to the starting material (by tlc).

b) Acetylation. A solution of the diacetate (16) (73mg) in pyridine (1ml) containing acetic anhydride (0.25ml) was allowed to stand for 25 mins at 100°. The reaction mixture was poured into water and the steroidal material, isolated using ether, was shown by tlc and NMR to be identical to the starting material.

Dehydration of the Triol-diacetate (16)

To a solution of the triol-diacetate (108mg) in pyridine (5 ml) was added thionyl chloride (0.5ml) at -20°. The mixture was allowed to stand at -20° for 15 mins and then poured into ether and water. The ethereal solution was washed with dilute HCl, NaOH solution and sodium bicarbonate solution. Removal of the solvent gave an oil (82mg), thought to be a mixture of the olefin diacetates (18a) and (19a), λ 200, ϵ 11,300; λ 220, ϵ 1600.

Hydrolysis of the Olefin-diacetates (18a & 19a)

The mixture of olefin-diacetates (82mg) was refluxed in ethanol (50ml) containing potassium hydroxide (150mg) for 2 hrs. Isolation via ether gave an oil (55mg), the olefin-diols (18b) and (19b), ν_{\max} 3620, 3350 cm^{-1} .

Ozonolysis of the Olefin-diols (18b & 19b)

The mixture of olefin-diols (35mg) was dissolved in chloroform (5ml) and cooled with dry ice-acetone. Ozone was passed through the solution for 45 mins, the chloroform removed under vacuum and the compound stirred with zinc (50mg) and acetic acid (5ml) for 2 hrs. Isolation via ether gave an oil (30mg), ν_{\max} 1730, 1720, 1707 cm^{-1} and a small peak ($-\text{CHO}$) at 2800 cm^{-1} . The NMR spectrum did not clearly show the presence of aldehyde.

Oxidation of the Olefin-diols (18b & 19b)

To a solution of the olefin-diol (20mg) in acetone (5ml) was added 8N chromic acid dropwise. The mixture was allowed to stand for 5 mins and then sodium metabisulphite added to decompose the excess chromic acid. Isolation via ether gave an oil (17mg), the diketones (21) and (22), ν_{\max} 1715, 1690 cm^{-1} ; λ_{\max} 245 $\text{m}\mu$ (ϵ 4700).

Hydrolysis of the Triol-diacetate (16)

A solution of the triol-diacetate (135mg) in ethanol (50ml) containing potassium hydroxide (200mg) was refluxed for 3½ hrs and then allowed to stand for 17 hrs at 20°. Isolation via ether gave the triol, an oil (105mg), ν_{\max} 3630, 3400 cm^{-1} .

Oxidation of the Triol

The triol (105mg) was dissolved in acetone (5ml) and oxidised with chromic acid. Isolation of the steroidal material using ether gave the diketone (23), an oil (77mg), ν_{\max} 1740 cm^{-1} .

Dehydration of the Diketone (23)

To a solution of the diketone (20mg) in pyridine (2ml) was added thionyl chloride (0.2ml) at -20° and the mixture allowed to stand at that temperature for 15 mins. Isolation via ether gave the olefin-diketones (21) and (22) as an oil, (15mg), ν_{\max} 1713, 1688 cm^{-1} ; λ_{\max} 237 $\text{m}\mu$ (ϵ 2940).

3-Keto-6 β -methylcholestan-5 α -ol (25)

A solution of 3 β -acetoxy-6 β -methylcholestan-5 α -ol (1d) in ethanol (200ml) containing potassium hydroxide (300mg) was allowed to stand at 25° for 64 hrs. The 3 β ,5 α -diol crystallised out and was isolated by filtration. Chromium trioxide (150mg) was added slowly to pyridine (3ml) and the mixture stirred for 1 hr. A solution of the diol (150mg) in pyridine (3ml) was added and the mixture left for 17 hrs at 20° . Isolation via ether gave 3-keto-6 β -methylcholestan-5 α -ol (25) as needles (130mg), m.p. $211-213^{\circ}$. (Lit²¹, m.p. $215-215.5^{\circ}$, $227-228^{\circ}$ (dec)).

Hydrolysis of the Olefin-diacetate (17a)

The reaction product (17a) (180mg) was dissolved in dry ether (5ml) and lithium aluminium hydride (200mg) added slowly. The mixture was allowed to stand at 20° for 2½ hrs and then at 5° for 17 hrs. Ethyl acetate was added dropwise until effervescence ceased, followed by water added dropwise to decompose the excess LiAlH_4 . The reaction mixture was poured into ether and water, washed with dilute NaOH solution and NaHCO_3 solution and the olefin-diol (17b) isolated as an oil (116mg), ν_{max} 3620, 3380 cm^{-1} .

Ozonolysis of the Olefin-diol (17b)

The olefin-diol (39mg) was dissolved in chloroform (5ml) and ozone bubbled through the solution for 1 hr at -78°. The chloroform was evaporated off under vacuum and the residue reacted with zinc (60mg) in acetic acid (5ml) for 2 hrs. Isolation via ether gave a ketone (20), ν_{max} 1707 cm^{-1} .

Oxidation of the Olefin-diol (17b)

The olefin-diol (33mg) was oxidised with 8N chromic acid in acetone. Isolation via ether gave the diketone (26) as an oil, ν_{max} 1738, 1704 cm^{-1} .

The diol (48mg) was reacted with chromium trioxide (50mg) in pyridine (4ml) for 17 hrs at 20°. Isolation via ether gave the olefin-diketone (26), an oil, ν_{max} 1736, 1708 cm^{-1} .

Attempted Isomerization of the Olefin-diketone (26)

A solution of the olefin-diketone (40mg), from oxidation with chromium trioxide-pyridine, in ethanol (10ml) containing oxalic acid (10mg) was refluxed for 30 mins. Isolation via ether gave an oil, ν_{\max} 1740, 1710 cm^{-1} . The product was reacted with sulphuric acid (3 drops) in ethanol (10ml) for 36 hrs. Isolation of the steroidal material gave an oil, ν_{\max} 1733, 1712 cm^{-1} . The ultraviolet spectrum showed no peak about 240 $\text{m}\mu$.

Oxymercuration-demercuration⁵⁵ of Cholest-5-ene

Cholest-5-ene (180mg) was added to a solution of mercuric acetate (160mg) in water (0.5ml) and tetrahydrofuran (3ml) and allowed to stand for 17 hrs at 40°. Sodium hydroxide solution (3N; 0.5ml) was added, followed by a solution of 0.5M sodium borohydride in 3N sodium hydroxide (0.5ml). The steroidal material was isolated via ether and appeared to be identical to the starting material (tlc, IR). The reaction was repeated replacing the tetrahydrofuran by dimethylsulphoxide but only the starting material was recovered.

Epoxidation of the Olefin-diacetate (17a)

The olefin-diacetate (200mg) was dissolved in chloroform (5ml) and a solution of monoperoxyphthallic acid (109mg) in ether (2.7ml) was added at 0°. The mixture was left at 20° for 24 hrs. The steroidal material was isolated via ether and did

not give any coloration with tetranitromethane.

Hydrolysis and Oxidation of the Epoxide

The epoxide from the above reaction (173mg) was dissolved in dry ether (5ml) and lithium aluminium hydride (280mg) added slowly. The mixture was allowed to stand for 17 hrs at 20°. Isolation via ether gave an oil (154mg) which was oxidised with 8N chromic acid in acetone. The product, isolated using ether, was an oil, ν_{max} 1830 cm^{-1} . The NMR spectrum indicated that the compound had decomposed.

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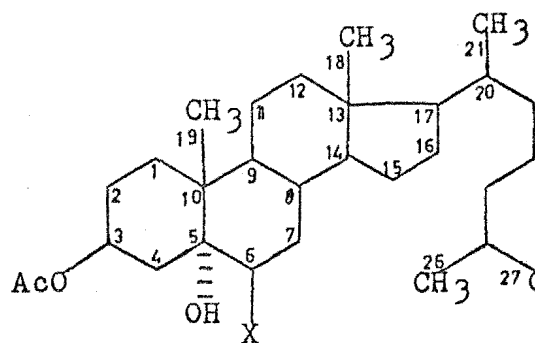
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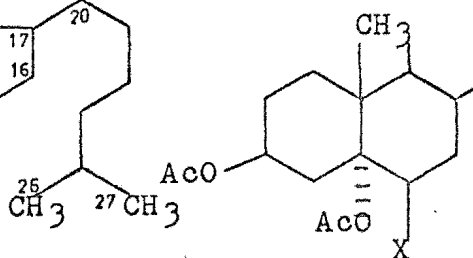
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ACKNOWLEDGEMENT

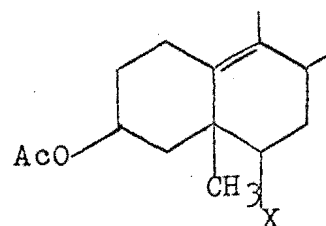
Acknowledgement is made to the Research Committee of the University Grants Committee for the award of a Postgraduate Scholarship.



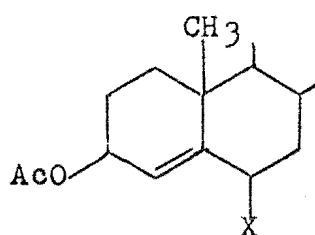
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 b X = OCH₃
 c X = H
 d X = CH₃



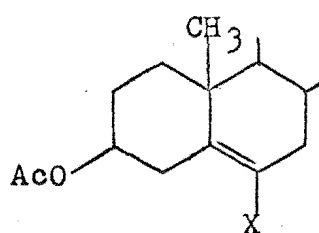
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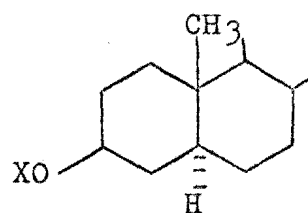
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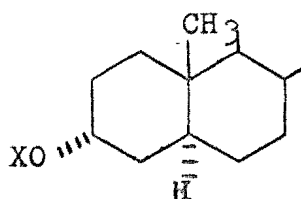
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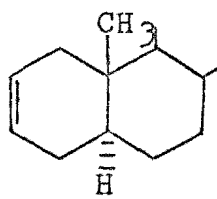
- (5) a X = H
 b X = CH₃



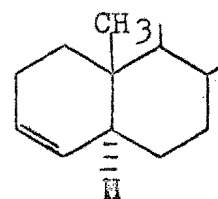
- (6) a X = H
 b X = Ac
 c X = HOSO₂
 d X = CH₃C₆H₄SO₂



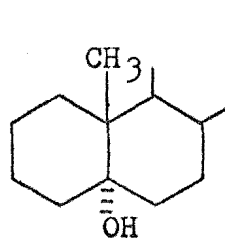
- (7) a X = H
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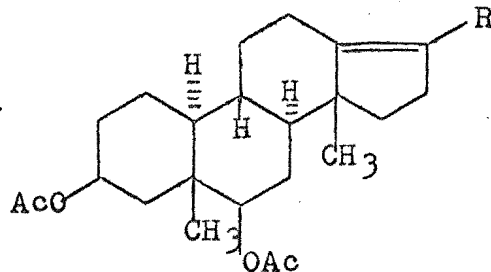
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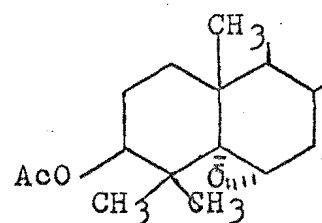
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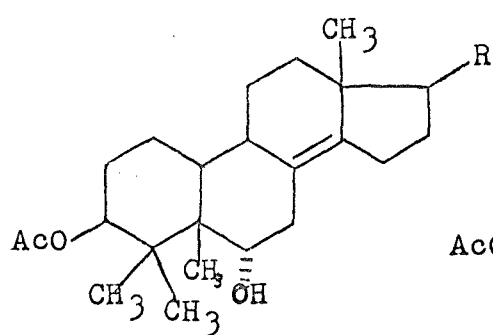
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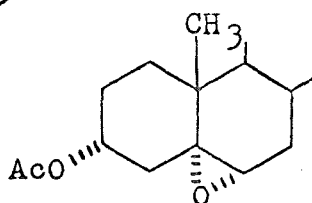
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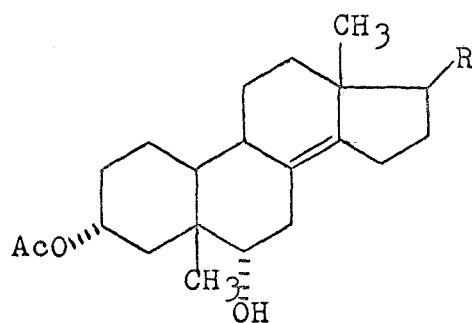
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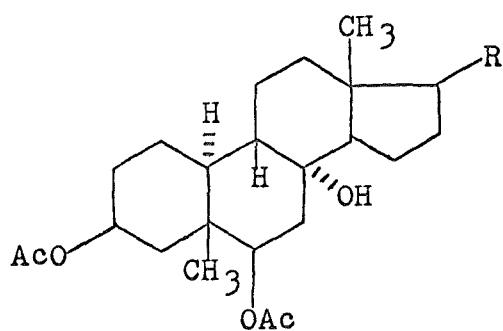
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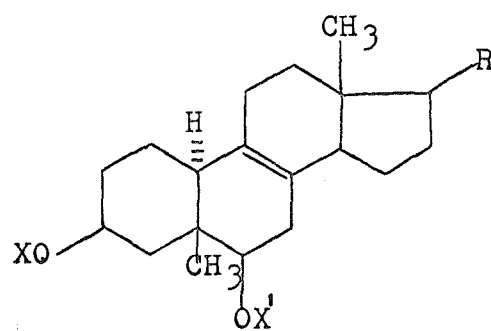
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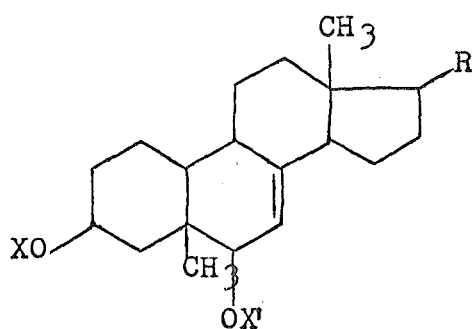
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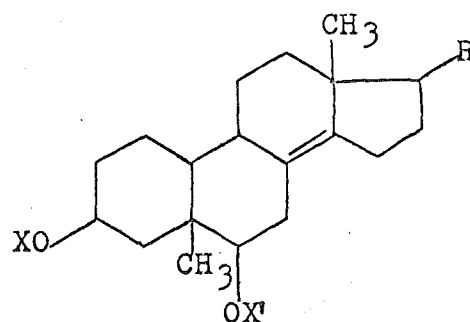
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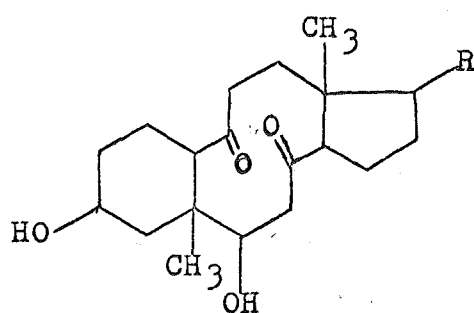
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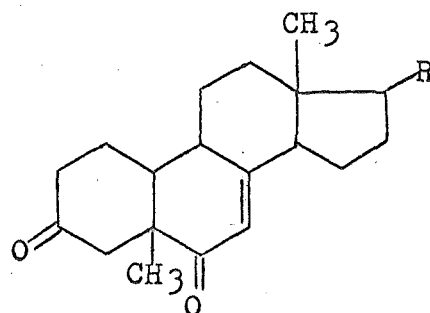
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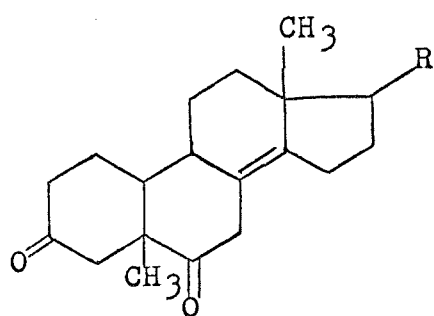
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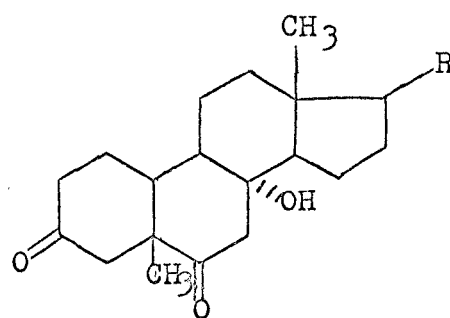
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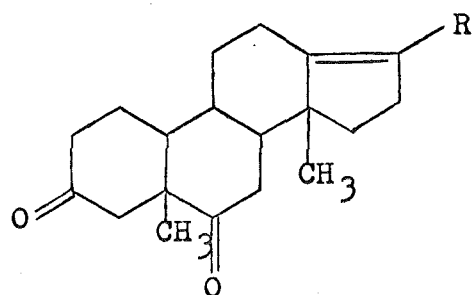
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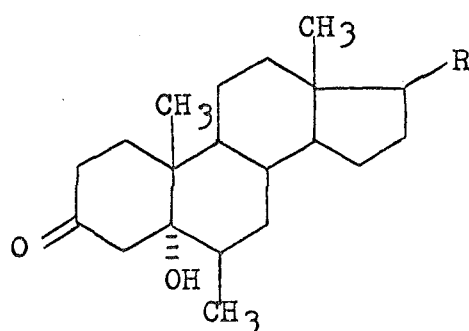
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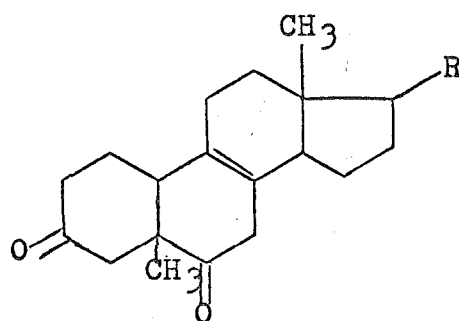
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(24)



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